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DISSEMINATED ENCEPHALOMYELITIS

A HISTOLOGIC SYNDROME ASSOCIATED WITH THROMBOSIS OF SMALL CEREBRAL VESSELS

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GENERAL CONCEPT OF "ENCEPHALITIS"

The term "encephalitis," according to Webster's dictionary, means "an inflammation of the brain." Inflammation is defined as "a morbid condition consisting in congestion of blood vessels and exudation of plasma and blood corpuscles at the site of an infection or injury." Most other lexicons concur in such a definition. Confusion has arisen because some pathologists use the term encephalitis as synonymous with infection of the brain. Since, in the group of diseases with which this paper will deal chiefly it is generally admitted that the anatomic changes observed coincide fairly well with the definition in the dictionaries, since the most important point at issue is exactly the question whether or not they are due to the presence of an infective agent within the brain and since, further, instances of these lesions are almost invariably indexed and catalogued under the denomination "encephalitis" or "encephalomyelitis," we shall continue to employ these terms to designate such conditions, without intending to imply more than that they fall within an anatomic category.

There have been many attempts to classify the "encephalitides." Oppenheim and Cassirer [1] divided them in general into an infectious and a toxic group, but saw little reason to distinguish between the two

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1. Oppenheim, H., and Cassirer, R.: Die Encephalitis, ed. 2, Vienna, A. Hölder, 1907.

on histologic grounds. A well known classification is that of Spatz,[2] in which an etiologic grouping is followed as far as possible and the remaining forms are arranged according to the portions of the brain chiefly involved. Marburg [3] and Ferraro [4] have considered chiefly the "encephalitides" involving the white matter and have both shown that there are definite transitions and similarities between types often described as separate entities.

A simple classification of the "encephalitides," which makes no claim to completeness, is given in the accompanying table. In the present paper we shall deal chiefly with the conditions of obscure nature and origin in group III, referring to groups I and II only for comparison. Specifically, we may take the "encephalomyelitis" which follows measles and vaccinia as illustrating the fundamental histologic changes occurring in the conditions in group III. Ferraro and Scheffer [5] described the lesions of postmeasles "encephalomyelitis" as follows:

> They consist mainly of a perivascular proliferation formed especially by microglial elements. The microglial nature of the cell is brought out beyond doubt by the specific method of silver impregnation.
>
> In some of the cases there were scattered elements of hematogenous nature in the perivascular areas. These elements were mainly lymphocytes, but occasionally plasma cells. The perivascular hematogenous elements were never of great importance, and in some cases there was no trace of them at all in all the material studied. The perivascular proliferation was dominantly located in the white matter, where it formed large islands. The cortex, however, was involved by the same process, although to a much less extent.
>
> Accompanying the perivascular proliferation there is a concomitant perivascular demyelinization, which forms another characteristic of the pathologic process. Lesions involving the axis cylinders are to be expected in demyelinated areas and have been reported in all our cases. Less characteristic is the macroglial reaction with both its progressive and its regressive changes. A fact that has not been emphasized sufficiently in the reports of other authors is the frequency of thrombi (red thrombi) and the occurrence of vascular changes, swelling or hyperplasia of the endothelium.

Globus [6] gave an essentially similar description of postvaccinal "encephalitis," though laying more emphasis on the hematogenous

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2. Spatz, H.: Encephalitis, in Bumke, O.: Handbuch des Geisteskrankheiten, Berlin, Julius Springer, 1930, vol. 11, p. 157.

3. Marburg, O.: Allgemeine Pathologie der nichteitrigen Entzündungen des Zentralnervensystems, Arb. a. d. neurol. Inst. a. d. Wien. Univ. **34**:1-22, 1932.

4. Ferraro, A.: Primary Demyelinating Processes of the Central Nervous System: An Attempt at Unification and Classification, Arch. Neurol. & Psychiat. **37**:1100-1160 (May) 1937.

5. Ferraro, A., and Scheffer, I. H.: Encephalitis and Encephalomyelitis in Measles: Pathologic Report of Six Cases, Arch. Neurol. & Psychiat. **25**:748-778 (April) 1931.

6. Globus, J. H.: Inflammatory Disease of the Central Nervous System: So-Called Nonsuppurative Encephalitis and Encephalomyelitis, Arch. Neurol. & Psychiat. **28**:810-843 (Oct.) 1932.

Classification of "Encephalitis" and "Encephalomyelitis" *

Group I. Infectious encephalitis
- Pyogenic
  - Abscess: Diffuse or localized
    - By continuity (from ear or sinus or following compound fracture; usually spreading along thrombosed veins)
    - Metastatic (embolic)
  - Meningitis (brain invaded only along thrombosed vessels)
- Infectious:
  - Due to recognized organisms
    - Syphilis: Meningeal or vascular (parenchymal damage by vascular occlusion)
      - Gumma (parenchymal damage by infiltration and by pressure)
      - Dementia paralytica (parenchymal damage usually attributed to invasion by spirochetes, but probably due to endarteritis of capillaries)
    - Tuberculosis: Solitary and conglomerate tubercles (damage to parenchyma by invasion, vascular thrombosis and pressure)
      - Meningitis (damage to parenchyma chiefly from thrombosis of vessels)
      - Diffuse tuberculosis of brain—rare (meningitis usually fatal before parenchyma is much involved)
    - Parasites: Invasion of brain by trypanosomes, trichinae, cysticerci, echinococci, etc.
  - Epidemic, can be transmitted to animals; essential feature is considered to be invasion of nerve cells by virus
    - Poliomyelitis
    - Rabies
    - Herpes febrilis
    - St. Louis type; Japanese type; Australian X disease
    - Certain diseases of animals, such as Borna disease, louping ill and distemper
  - Presumably infectious (epidemic, but never satisfactorily transmitted to animals)
    - "Encephalitis lethargica" ("epidemica," von Economo's disease): One recognized pandemic in 1918-1924, followed (and preceded?) by sporadic cases. Basal gray matter chiefly involved, but white matter also suffers; characteristic vascular degeneration, pseudocalcium deposits, lymphocytic exudation, even in late stages; massive foci of pure oligodendroglial and microglial proliferation, ependymitis
  - Herpes Zoster (zona)

Group II. "Encephalitis" definitely not of infectious origin (encephalopathy)
- Symptomatic: Inflammatory phenomena, often appearing in spinal fluid as well as in brain, accompanying softenings, tumors, mechanical and electrical trauma, etc.
  - "Chronic subcortical encephalitis" (Binswanger)
- Toxic:
  - Alcohol—Polioencephalitis superior haemorrhagica of Wernicke; vascular degenerations, accompanied by hemorrhages and adventitial and glial proliferation. Vitamin B deficiency(?)
  - Lead—Proliferative endarteritis; degeneration chiefly of gray matter; pseudocalcium deposits
  - Carbon Monoxide—Scattered lesions in gray and white matter, sometimes only in globus pallidus
  - Methyl alcohol—Often most intense in globus pallidus
  - Benzene—Most lesions dependent on venous thromboses
  - Arsenic (arsphenamine)—Diffuse hemorrhagic lesions, chiefly in white matter
  - Many other poisons
- Deficiency disease:
  - Pellagra (and pellagroid degenerations accompanying chronic alcoholism, etc.)
  - Encephalopathy of pernicious anemia (?) and other deficiency diseases
- Vascular complications of infectious diseases (see also "disseminated encephalomyelitis," group III)
- Sydenham's chorea (and other complications of endocarditis)
- Cerebral manifestations of whooping cough, mumps, malaria, typhoid, typhus, yellow fever and dysentery

Group III. "Disseminated encephalomyelitis" (leukoencephalitis): A large group of diseases characterized by a fairly definite pathologic picture
1. Lesions predominate in the white matter
2. Lesions tend to occur around engorged veins, though they may coalesce
3. Lesions are characterized chiefly by myelin destruction and glial proliferations, but lymphocytic and hemorrhagic diapedesis may occur
4. Thrombosis of vessels is constantly observed in the acute stage and is presumably the origin of the changes in the parenchyma

The cause is varied. In the majority of instances there is no history of an acute infection. Instances of spread from one patient to another have never been reported. Occasionally the nervous symptoms occur at the height of immunity to an acute disease, as in the postmeasles and postvaccinal forms, which are of this type.

- Postinfectious (measles, smallpox, vaccinia, rubella, antirabic inoculations)
- Acute transverse myelitis ("idiopathic," relapsing central necrosis, myelomalacia). Often accompanied by smaller lesions in the brain
- Perivenous encephalitis
- Purpura of the brain, hemorrhagic encephalitis (in some cases obviously of toxic origin, e. g., due to arsphenamine)
- Periaxial encephalitis (Schilder's disease, diffuse sclerosis in late state)
- Acute multiple sclerosis
- Chronic subcortical encephalitis (Binswanger)
- Multiple degenerative softening
- Neuromyélite optique

Group IV. Miscellaneous and unclassified types
- Encephalitis neonatorum
- "Serous encephalitis"

* Inclusive terms for diseases of the central nervous system characterized pathologically by exudation of cells of hematogenous origin and proliferation of the glia.

elements. He stated that later in the course of postmeasles "encephalitis" "the mesodermal reaction disappears rapidly, and instead the glial reaction dominates the scene."

For the purposes of this paper, we may describe the various phases of this whole process as the "encephalomyelitic reaction." In general, the perivascular collection of microglia and hematogenous cells predominates in or near the gray matter and the diffuse macroglial reaction in the white matter (Spielmeyer [7]).

MECHANISM OF THE "ENCEPHALOMYELITIC REACTION"

Recent investigations have shown that this reaction can be produced experimentally in animals. Apparently, Claude [8] was the first to observe it after the intramuscular administration of tiny doses of tetanus toxin. His experiments were successfully repeated in this laboratory.[9] Ceni and Besta [10] described the reaction after inoculation with Aspergillus fumigatus. Meyer produced it with carbon monoxide poisoning,[11] and Ferraro, with chronic cyanide poisoning.[12] Rivers and Schwentker [13] observed a somewhat similar histologic picture after repeated injections of brain extract. It has also been produced mechanically, by simple obstruction of cerebral venules.[14]

Prompted by the observation last mentioned and certain theoretic considerations, Hoefer, Putnam and Gray [15] carried out a series of investigations on the cerebral lesions produced by the intravenous administration of a variety of coagulants. The effect on other organs has been

7. Spielmeyer, W.: Infektion und Nervensystem, Ztschr. f. d. ges. Neurol. u. Psychiat. **123**:161-203, 1930.

8. Claude, H.: Myélite expérimentale subaiguë par intoxication tétanique, Arch. de physiol. norm. et path. **29**:843-847, 1897.

9. Putnam, T. J.; McKenna, J. B., and Evans, J.: Experimental Multiple Sclerosis in Dogs from Injection of Tetanus Toxin, J. f. Psychol. u. Neurol. **44**: 460-467, 1932.

10. Ceni, C., and Besta, C.: Sclerocci in placche sperimentale da tossici asperigillari, Riv. sper. di freniat. **31**:125-135, 1905.

11. Meyer, A.: Experimentelle Erfahrungen über die Kohlenoxydvergiftung des Zentralnervensystems, Ztschr. f. d. ges. Neurol. u. Psychiat. **112**:187-213, 1928.

12. Ferraro, A.: Experimental Toxic Encephalomyelopathy: Diffuse Sclerosis Following Subcutaneous Injections of Potassium Cyanide, Arch. Neurol. & Psychiat. **29**:1364-1365 (June) 1933.

13. Rivers, T., and Schwentker, F. F.: Encephalomyelitis Accompanied by Myelin Destruction Experimentally Produced in Monkeys, J. Exper. Med. **61**: 689-702, 1935.

14. Putnam, T. J.: Studies in Multiple Sclerosis: "Encephalitis" and Sclerotic Plaques Produced by Venular Obstruction, Arch. Neurol. & Psychiat. **33**:929-940 (May) 1935.

15. Hoefer, P. F. A.; Putnam, T. J., and Gray, M. G.: Experimental "Encephalitis" Produced by Intravenous Injection of Various Coagulants, Arch. Neurol. & Psychiat. **39**:799-812 (April) 1938.

well described by Kusama [16] and others. In this laboratory, the most uniformly successful and easily controlled coagulant was found to be Mill's lung extract. Entirely comparable results were produced, however, with heterologous serums and bacterial suspensions and washings.

In acute experiments, thrombi which corresponded entirely to Kusama's description were seen in the brain. Their efficacy as obstacles to circulation was proved by subsequent injection of india ink. If sublethal doses of coagulant were given and the animal was permitted to live, lesions developed in the course of a few days or weeks which closely simulated the "encephalomyelitic reaction." The animals could be made resistant to several times the fatal dose of lung extract by previous treatment with an anticoagulant, such as cystein. It was found that the brain extract employed by Rivers and Schwentker [18] to produce "encephalomyelitis" was an active coagulant.

Studies of human pathologic material have also revealed evidence that the "encephalomyelitic reaction" may be produced by a variety of types of vascular obstruction in the central nervous system.[17] An example in group III of the present classification is the "chronic subcortical encephalitis" first described by Binswanger,[18] which both he and, later, Farnell and Globus [19] unhesitatingly ascribed to sclerosis of small vessels of the white matter.

SCOPE OF THE PRESENT INVESTIGATION

In view of the numerous evidences that the "encephalomyelitic reaction" can be produced by various types of vascular, especially venular, occlusion, survey of histologic material in cases of "encephalitis" of different types was undertaken to observe in which the reaction occurred at all and in which it constituted the predominant or sole lesion. Further, an especial search was made for thrombi and other endovascular changes. A similar investigation on the histologic changes in multiple sclerosis has recently been reported on.[20]

Before proceeding to a description of the individual diseases, it may be well to consider in more detail what constitutes a thrombus. This

16. Kusama, S.: Ueber Aufbau und Entstehung des toxischen Thrombose und deren Bedeutung, Beitr. z. path. Anat. u. z. allg. Path. **55**:459-544, 1913.

17. Putnam, T. J., and Alexander, L.: Tissue Damage Resulting from Disease of Cerebral Blood Vessels, A. Research Nerv. & Ment. Dis., Proc. **18**:544-567, 1938.

18. Binswanger, O.: Die Abgrenzung des allgemeinen progressiven Paralyse, Berl. klin. Wchnschr. **31**:1187, 1894.

19. Farnell, F. J., and Globus, J. H.: Chronic Progressive Vascular Subcortical Encephalopathy: Chronic Progressive Subcortical Encephalitis of Binswanger, Arch. Neurol. & Psychiat. **27**:593-604 (March) 1932.

20. Putnam, T. J.: Evidences of Vascular Occlusion in Multiple Sclerosis and "Encephalomyelitis," Arch. Neurol. & Psychiat. **37**:1298-1321 (June) 1937.

question, simple as it sounds, is often surprisingly difficult to answer. The descriptions in textbooks of thrombi in large vessels have hardly any application to clots in small vessels. The pathologist who would familiarize himself with the subject should study the appearance of experimentally produced thrombi [15] and those in the neighborhood of abscesses and incisions in the brain. According to Johnson,[21] Tannenberg [22] and others, the first stage in the formation of a thrombus at a point of injury to the wall of the vessel or about a foreign body is agglutination of platelets. In Kusama's [16] preparations and in the experiments of Hoefer and his associates,[15] the thrombosis which occurs without an antecedent injury to endothelium also usually starts by agglutination, but actual precipitation of protein masses without formed elements may also occur. Either process is more likely to be observed on the venous side of the capillary net than in arteries. Distention of the vessel, the formation of curved strands of fibrin, adhesion of the mass to the endothelium and edema of the wall of the vessel are common subsequent stages. A characteristic picture, presumably to be interpreted as thrombosis, is the distention of capillaries by homogeneous masses of fibrin and cells. Brittle-looking masses of red cells, partly hemolyzed, in the segment proximal to the obstruction may be taken as presumptive evidence of thrombosis.

With all these criteria, it is often impossible to be sure that a given mass in a vessel is a thrombus. When any of them occur, however, it is impossible to predicate that the clot in question is not a thrombus.

Whatever the primary cause of obstruction, the resulting changes in the adjacent vascular bed are the same. There is passive dilatation of the proximal vessels up to the next anastomosis, often with diapedesis of red and white blood cells and partial collapse of distal communications.[23]

The contents of small thrombosed vessels undergo a series of changes which is different from that seen in thrombi in the aorta and heart, in which the circulation can continue past the vegetation for a time. Thrombi in small vessels, on the contrary, usually either redissolve and disappear (Kusama [16]) or lead to necrosis of the wall of the vessel.[24] The closely packed cells in the distended proximal segment gradually hemolyze, conglutinate and liquefy.

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21. Johnson, W. R.: Experimental Thrombosis: The Appearance of Fibrin in the Early Stages of Formation of White Thrombus, Folia haemat. **48**:413-432, 1932.

22. Tannenberg, J.: Experimental Studies on Primary Changes During the Formation of Thrombi, Arch. Path. **23**:307-315 (March) 1937.

23. Alexander, L., and Putnam, T. J.: Pathologic Alterations of Cerebral Vascular Patterns, A. Research Nerv. & Ment. Dis., Proc. **18**:471-543, 1938.

24. Campbell, A. C. P.; Alexander, L., and Putnam, T. J.: Vascular Pattern in Various Lesions of the Human Central Nervous System: Studies with the Benzidine Stain, Arch. Neurol. & Psychiat. **39**:1150-1202 (June) 1938.

Whatever damage has been done to the surrounding parenchyma runs its course. Collateral circulation is reestablished by dilation of tributaries, but the characteristic gnarled tortuosity is slow to disappear.[24]

Yellow pigment containing iron appears early in the progress of the obstruction and persists a surprisingly long time. Some alteration of capillary architecture is, however, probably as permanent as the parenchymal damage.[23]

THE "ENCEPHALOMYELITIC REACTION" IN INFECTIOUS ENCEPHALITIS

One of the reasons that the "encephalomyelitides" of the third group have been considered to be of infectious origin is that a similar histologic syndrome may be observed in practically all cases of infection of the brain. Closer examination shows, however, that when such a reaction occurs damage to the blood supply can usually be demonstrated.

This is clearly illustrated by a case of extensive subdural abscess of five weeks' duration, in which the spinal fluid was sterile at the time of death. Several small areas of "encephalomyelitis" consisting of perivenous areas of demyelination and glial proliferation, with occasional vessels infiltrated with phagocytes and cells resembling lymphocytes, were seen scattered throughout the brain. One of them occurring in the pons is illustrated in figure 1. The blood vessels in the vicinity of the lesion are engorged, tortuous and in some places apparently obstructed by hyaline masses (fig. 2), and there is much hematogenous pigment about them.

Similar areas are familiar in the white matter in cases of dementia paralytica, and their resemblance to the plaques of multiple sclerosis has long since been pointed out by Spielmeyer [25] and by Bielschowsky.[26] Recent evidence suggests that not only these but the areas of cortical atrophy may be due to a primary vascular closure.[27] In such cases the vascular occlusion is probably to be ascribed to endothelial hypertrophy rather than to thrombosis. In certain cases of pyogenic meningitis, and also sometimes in tuberculous meningitis, however, thrombosis of parenchymal vessels may occur and produce a typical "encephalomyelitic reaction." This has been noted by Wertham,[28] and further examples are given elsewhere.[23]

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25. Spielmeyer, W.: Ueber einige anatomische Aehnlichkeiten zwischen progressive Paralyse und multiple Sklerose, Ztschr. f. d. ges. Neurol. u. Psychiat. **1**:660-694, 1910.

26. Bielschowsky, M.: Ueber Markfleckenbildung und spongiösen Schichtenschwund in des Hirnrinde des Paralytikers, J. f. Psychol. u. Neurol. **25**:72-100, 1919.

27. Merritt, H. H.; Putnam, T. J., and Campbell, A. C. P.: Pathogenesis of the Cortical Atrophy Observed in Dementia Paralytica, Arch. Neurol. & Psychiat. **37**:75-90 (Jan.) 1937.

28. Wertham, F.: Cerebral Lesions in Purulent Meningitis, Arch. Neurol. & Psychiat. **26**:549-582 (Sept.) 1931.

THE "ENCEPHALOMYELITIC REACTION" IN THE EPIDEMIC ENCEPHALITIDES

In the lethargic encephalitis described by von Economo, the lesions are usually described as being confined to the gray matter and are characterized by "cuffing" of small vessels, chiefly with lymphocytes. A certain amount of degeneration of myelin and glial proliferation may, however, occur in the white matter. Peters [29] and de Wulf and van Bogaert [30] reported cases in which the lesions of epidemic encephalitis

Fig. 1.—Focus of demyelination and glial proliferation in the pons, in a case of extensive subdural abscess, in which the spinal fluid was sterile. Hematoxylin and eosin; lens enlargement.

were accompanied by typical sclerotic plaques. The presence of thrombi has been recorded by Stern,[31] and several authors have reported malacic lesions.

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29. Peters, G.: Ueber das gemeinsame Vorkommen von Encephalitis epidemica und multiple Sklerose, Deutsche Ztschr. f. Nervenh. **138**:23-33, 1935.

30. de Wulf, A., and van Bogaert, L.: Une association anatomo-clinique exceptionelle: Encéphalite épidémique et sclerose en plaques, Ann. de méd. **39**:417-434, 1936.

31. Stern, F.: Epidemische Encephalitis (Economo's Krankheit), in Bumke, O., and Foerster, O.: Handbuch der Neurologie, Berlin, Julius Springer, 1936, vol. 13, p. 406.

In a recent case in which the disease ran a course compatible with that of the choreic form of epidemic encephalitis, autopsy revealed lesions of the putamen, caudate nucleus, globus pallidus, optic thalamus, red nucleus and substantia nigra, characterized by scattered lymphocytic infiltration and necrosis of ganglion cells (severe cell disease). A few other lesions with focal lymphocytic infiltration and glial proliferation were seen in the internal and external capsule, but in no other part of the white matter. Thrombi occurred in connection with both. They were made up of dense clumps of platelets, about which had formed a network of fibrin. Necrosis of some vessels had occurred (fig. 3).

Lesions of the basal ganglia, closely resembling those of epidemic encephalitis, with lymphocytic "cuffing" of vessels, "pseudocalcification" of walls of the vessels, ependymal granulations and subependymal gliosis, have recently been seen in 2 other cases in this laboratory. One was a case of nitrogen monoxide poisoning in which the patient survived three days.[32] In this instance, the changes were

Fig. 2.—Thrombosed vein in the same case of subdural abscess illustrated in figure 1. Mallory stain; 8 mm. lens.

obviously secondary to numerous degenerating thrombi (fig. 4), which were seen also in other organs. The second case was one of multiple embolism resulting from endocarditis, in which foci of true softening with mobilization of scavenger cells also occurred.

The question may fairly be raised, therefore, whether the histologic appearance of the lesions of epidemic encephalitis can be taken as evidence that the disease is due to the presence of an infectious agent in the brain. The epidemic nature of the disease has been universally accepted, but none of Koch's postulates have been satisfied in regard to it.

32. Putnam, T. J.: The Cerebral Circulation: Some New Points in Its Anatomy, Physiology and Pathology (E. Bates Block Memorial Lecture), J. Neurol. & Psychopath. **17**:193-212, 1937.

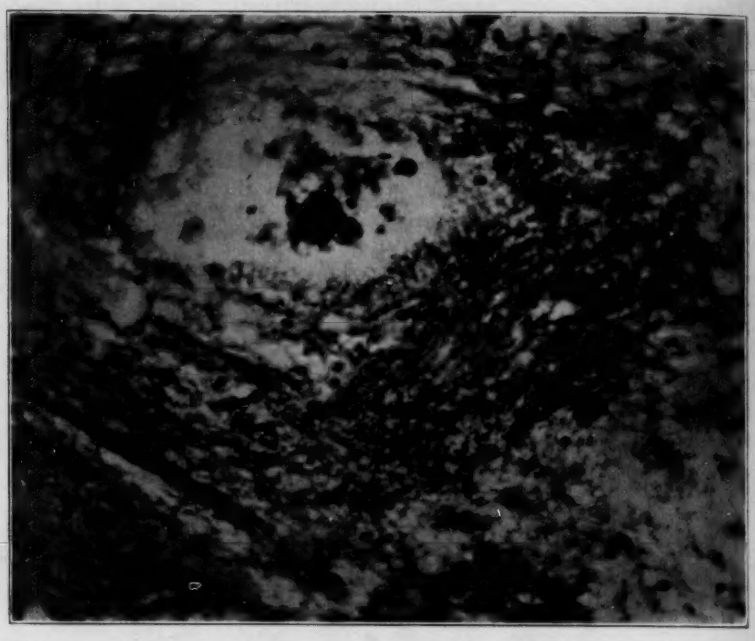

Fig. 3.—Necrotic vessel in a case of encephalitis lethargica. Masson stain; 8 mm. lens.

Fig. 4.—Thrombus consisting of degenerating cells enmeshed in heavy, curved strands of fibrin, distending a vessel the walls of which show "pseudocalcification," in a case of late death after nitrogen monoxide poisoning. Hematoxylin and eosin stain; oil immersion.

A similar histologic reaction has been described in the recent epidemic of encephalitis seen first in St. Louis. In the lesions of this disease, also, the "encephalomyelitic reaction" occurred in the white matter, while the lesions in the gray matter were more usually marked by perivascular accumulations of cells.[33] The thrombi seen in association with them consisted of hyaline masses almost filling the lumen, with only moderate agglutination of platelets and deposit of fibrin. One vessel was observed to have disintegrated entirely for a distance of 0.5 cm., leaving only a deposit of blood pigment (fig. 5).[34]

In this disease also, then, conclusive evidence of the existence of an infectious agent in the central nervous sytem is not afforded by the histologic appearance of the lesions. Transmission to animals has been reported, but the validity of the results has been criticized.[35]

The lesions characteristic of poliomyelitis and of rabies, respectively, are sufficiently distinct from those of the "encephalomyelitides" under discussion that we need not consider them here.

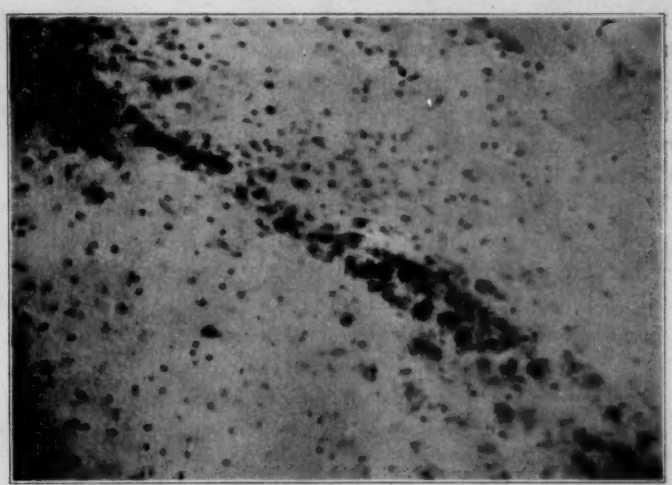

Fig. 5.—Line of yellow hematogenous pigment, apparently the remnant of a thrombosed and necrotic vessel surrounded by diffuse glial proliferation, in a case of the St. Louis type of "encephalitis." Gallocyanine stain; 16 mm. lens.

THE "ENCEPHALOMYELITIC REACTION" IN THE NONINFECTIOUS ENCEPHALOPATHIES

Two examples of the "encephalomyelitic reaction" in diseases definitely not of infectious origin have already been alluded to. One

33. McCordock, H. A.; Collier, W., and Gray, S. H.: Pathologic Changes of the St. Louis Type of Acute Encephalitis, J. A. M. A. **103**:822-824 (Sept. 15) 1934.

34. These observations were made in a case from which Dr. Sydney Schwab sent material.

35. Löwenberg, K., and Zbinden, F.: Epidemic Encephalitis (St. Louis Type) in Toledo, Ohio, Arch. Neurol. & Psychiat. **36**:1155-1165 (Dec.) 1936.

is the case of "subcortical encephalitis" of Binswanger, with an arteriosclerotic basis; the other is a case of nitrogen monoxide poisoning. The sequence of events in carbon monoxide poisoning [32] and in a variety of other noninfectious lesions [17] has been considered elsewhere. Spielmeyer,[7] Cone and Barrera,[36] Ch'eng [37] and Bertrand and Miyashita [38] have recorded many examples of "inflammatory" infiltration in purely degenerative conditions.

THE "DISSEMINATED ENCEPHALOMYELITIDES"—POSTINFECTIOUS TYPE

Finally, we come to the third group in our classification, which is really the one under consideration in this paper. The group in question is one the boundaries of which are ill defined, but its prototypes may well be taken to be the postmeasles and postvaccinal "encephalitides," the histologic changes in which have already been characterized. The frequent occurrence of thrombi in cerebral veins and in the sinuses in such cases has been mentioned by Ferraro and Scheffer [5] and has been considered in more detail in an unpublished paper by Kreider,[39] from the same laboratory. Further references bearing on this subject are given in a previous paper.[20] These authors described brittle-looking masses in hugely distended vessels. Von Herkenrath [40] described a lesion which was obviously of vascular origin in a case of postvaccinal "encephalitis" of long standing. One of us (T. J. P.) has elsewhere [20] given a preliminary account of leukocytic and fibrinous thrombi also, demonstrated by stains of the Masson and Mallory type. Finley [41] recently adduced evidence that the formation of "encephalitic" lesions of these two types is in some sense an allergic rather than an infectious process, as its outbreak corresponds precisely with the development of immunity.

In the present investigation, isolated blocks of material in 3 cases of postvaccinal and in 4 of postmeasles "encephalitis" were available for study.[42] In all

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36. Cone, W., and Barrera, S. E.: The Brain and the Cerebrospinal Fluid in Acute Aseptic Cerebral Embolism: An Experimental and Pathologic Study, Arch. Neurol. & Psychiat. **25**:523-547 (March) 1931.

37. Ch'eng, Y. L.: Symptomatic Inflammation, Arch. Neurol. & Psychiat. **31**:1247-1257 (June) 1934.

38. Bertrand, I., and Miyashita, K.: Varibilité des périvascularites au cours des encéphalites, Presse méd. **44**:491-494, 1936.

39. Kreider, P.: Measles Encephalomyelopathy with Venous Thrombosis, unpublished data.

40. von Herkenrath, B.: Pathologisch-anatomisch gesicherte Ausheilung eines Falles von Encephalitis post vaccinationem, Ztschr. f. d. ges. Neurol. u. Psychiat. **152**:293-300, 1935.

41. Finley, K. H.: The Pathogenesis of Encephalitis Occurring with Vaccination, Variola and Measles, Arch. Neurol. & Psychiat. **39**:1047-1054 (May) 1938.

42. Material in 1 of these cases was contributed by Dr. Timothy Leary, that in 3 others by Dr. R. D. Lillie, of the Public Health Service, and that in 2 by Dr. Nicholas Malamud.

these cases the lesions were irregularly disseminated and grouped about distended veins and consisted of areas of demyelination with relative integrity of axis-cylinders. The "inflammatory" phenomena were extremely variable in intensity, however. In a case of postvaccinal "encephalitis," in which considerable material was available, the areas of demyelination contained only degenerating red cells and fibrin. No lymphocytic infiltration and only minimal diffuse astrocytic response was visible. In the other cases there were exhibited varying degrees of intra-adventitial infiltration and glial proliferation, such as have been described by Ferraro and Scheffer [5] and by Globus,[6] in the sections quoted, and recorded by many others.

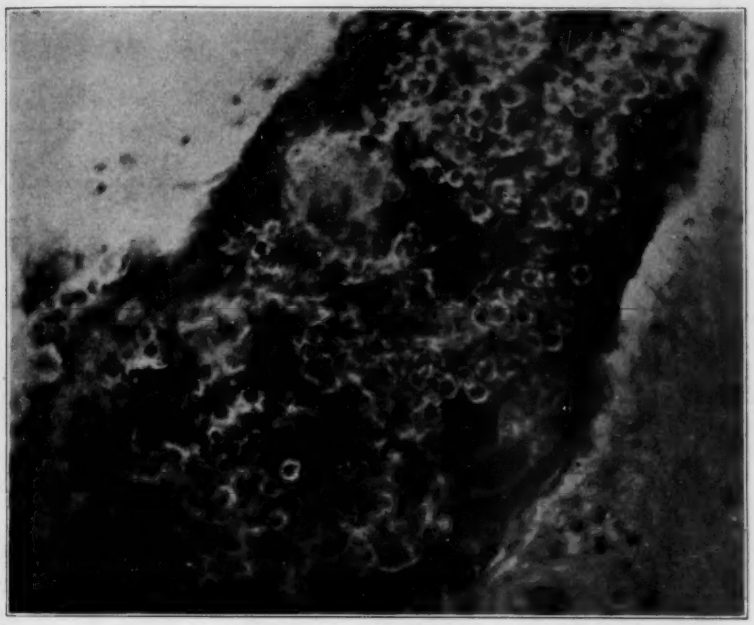

Fig. 6.—Thrombus in a cerebral vein in a case of postvaccinal "encephalitis," consisting of masses of coagulum distending the vessel. Note the necrosis of the wall. Masson stain; oil immersion.

The thrombi observed in all 6 cases of this type studied were of the varieties already described. The packed, brittle-looking, partly hemolyzed masses of red cells described by Ferraro and Scheffer were common. There were also masses suggestive of platelets embedded in coarse, curving bands of fibrin, which stained blue with Mallory's connective tissue stain (fig. 6). In 1 case of postmeasles "encephalitis," examination of sections from other organs revealed numerous thrombi (fig. 7).

The "virus" diseases are not the only precursors of lesions of the type described. "Encephalomyelitis" also occurs as a complication of pneumonia and

other bacterial infections[43] and may follow the administration of proteins.[44] It has followed such exogenous accidents as burns.[45] In our material, precisely similar lesions were seen in 2 cases of "encephalitis" following tonsillitis and sinusitis, respectively. Here, also, intra-adventitial collections of microglia cells and occasional lymphocytes and leukocytes alternated with more diffuse proliferation of fixed glia cells (fig. 8*A*). The accompanying thrombi were of the same type as those seen in cases of postvaccinal "encephalitis" (fig. 8*B*). Cultures of the brain were sterile, and no organisms were seen in the lesions with bacterial stains. In 1 of these cases (and not in the others) other organs were available for study; they showed thrombi.[46]

"ENCEPHALOMYELITIS" FOLLOWING ANTIRABIC INOCULATION

The question whether the "encephalitis" and "myelitis" which occasionally follow the Pasteur treatment are similar to the condition

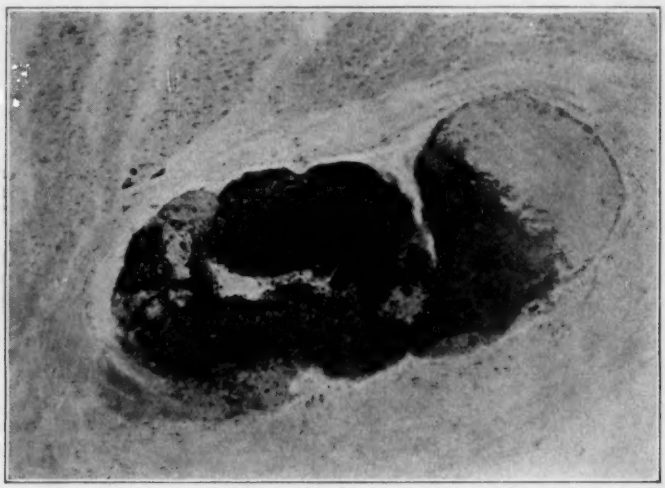

Fig. 7.—Thrombus, consisting of a dense network of curved strands of fibrin, distending a vein with necrotic walls, in the heart muscle in a case of postmeasles "encephalomyelitis." Hematoxylin and eosin stain; low power lens.

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43. Gray, L. A.: Myelitis and Encephalomyelitis Associated with Gonorrhea, Am. J. Syph., Gonor. & Ven. Dis. **21**:50-63, 1937. Davison, C., and Brock, E.: Acute Demyelinating Encephalomyelitis Following Respiratory Disease, Bull. Neurol. Inst. New York **6**:504-518, 1937.

44. Winkelman, N. W., and Gotten, N.: Encephalomyelitis Following the Use of Serum and Vaccine: Report of Two Cases, One with Autopsy, Am. J. Syph. & Neurol. **19**:414-424, 1935.

45. Globus, J. H., and Bender, M. B.: Disseminated Toxic Degenerative Encephalopathy (Disseminated Sclerosing Demyelination) Secondary to Extensive and Severe Burns, J. Nerv. & Ment. Dis. **83**:518-529, 1936.

46. Putnam, T. J.: Lesions of "Encephalomyelitis" and Multiple Sclerosis: Venous Thrombosis as the Primary Alteration, J. A. M. A. **108**:1477-1480 (May 1) 1937.

just described remains open. The lesions resemble somewhat those of rabies, but they lie chiefly in the white matter. Rivers and Schwentker [18] produced somewhat similar areas of demyelination, with a peculiar cel-

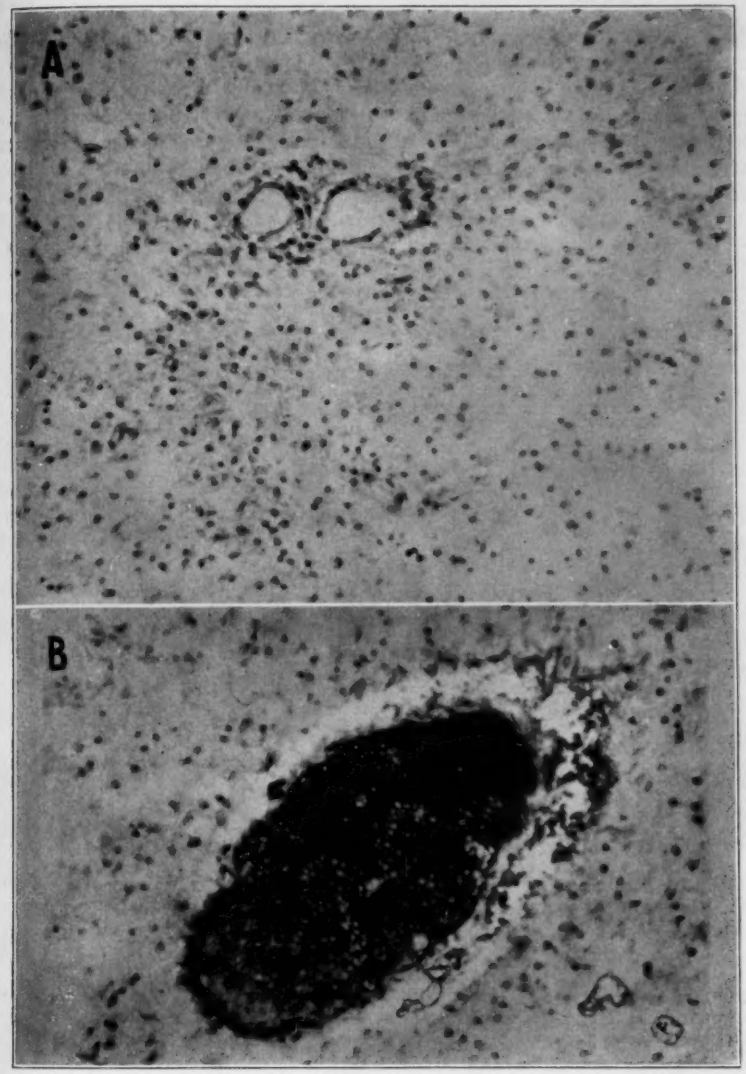

Fig. 8.—*A*, intra-adventitial infiltration and diffuse glial proliferation in a case of "encephalitis" following tonsillitis. Nissl stain; 16 mm. lens. *B*, mural thrombus in a cerebral vein in the same case as that illustrated in *A*. Masson stain; 8 mm. lens.

lular response which includes some multinucleated cells, by injection of brain extracts, and expressed the belief that the process is allergic

rather than infectious. Hoefer, Putnam and Gray,[15] however, found that the brain extract used is an active coagulant and suggested that the phenomenon belongs with the other experimental "encephalomyelitides" produced by coagulant substances.

In 2 cases of "encephalomyelitis" following antirabic treatment,[47] the lesions were seen chiefly in the white matter in the vicinity of the nuclei of the cerebellum and pons (the only regions available for study). Bassoe and Grinker[48] observed similar lesions. They consisted chiefly of heavy lymphocytic cuffs, with little diffuse glial response. The associated thrombi were in part of the type described for the postmeasles and postvaccinal "encephalomyelitides." In addition, vessels were seen the lumen of which was largely filled with globules, from 2 to

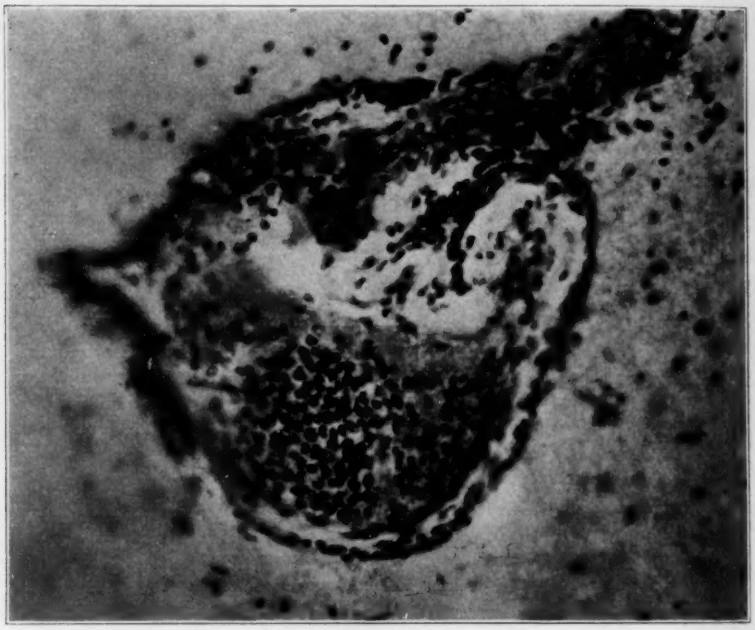

Fig. 9.—Thrombus in a cerebral vein in a case of "encephalitis" following antirabic inoculation. The lumen is entirely filled with polycytes adherent to curved strands of fibrin. Thionine stain; 8 mm. lens.

20 microns in diameter, of a hyaline appearance, which stained red with the Masson and Mallory stains.[46] There were also thrombi consisting of masses of polycytes adherent to curved strands of fibrin (fig. 9).

SIMILAR "ENCEPHALOMYELITIDES" OF OBSCURE ORIGIN

Although the cases of postinfectious "encephalitides" have received much attention because of the dramatic history, they are probably out-

47. Dr. R. D. Lillie, of the Public Health Service, contributed this material.

48. Bassoe, P., and Grinker, R. R.: Human Rabies and Rabies Vaccine Encephalomyelitis: A Clinicopathologic Study, Arch. Neurol. & Psychiat. **23**: 1138-1160 (June) 1930.

numbered by those of the clinically and pathologically similar "encephalitides" for which no cause is obvious.

Four such cases were observed in the present study. In 2 of them the disease ran an acute course, and the lesions were similar to those described for the postinfectious forms. Thrombi consisting of platelets and curved strands of fibrin were the rule, although in 1 instance an extraordinary mass of fresh fibrin staining red with fuchsin was observed.

In the third case (furnished by Dr. Bernard Alpers) the condition was obviously more chronic, and there were lesions resembling early sclerotic plaques (fig. 10*A*) as well as those containing vessels densely infiltrated with microglia and hematogenous cells and an intense diffuse glial proliferation (fig. 10*B*). Early thrombi, consisting of agglutinated platelets, were observed, and also older thrombi, in which there were necrosis of the wall of the vessel and invasion of the clot (fig. 11).

In the fourth case there was a history of gradual deterioration and somnolence over several years, somewhat suggesting lethargic "encephalitis." At autopsy multiple small hyaline capillary thrombi and some large thrombosed veins (fig. 12*A*) were seen scattered throughout the brain. In association with them were many punctate hemorrhages, some fresh, some old. A small area of demyelination corresponded to each, only the older lesions having called forth a mild glial response (fig. 12*B*). The lesions were most numerous in the thalamus. They resembled precisely those seen in 1 of the instances of postvaccinal "encephalomyelitis" already mentioned, a similarity which constitutes the chief justification for including the case in the series.

MULTIPLE SCLEROSIS AND "ACUTE MULTIPLE SCLEROSIS"

Evidence has been given elsewhere [49] which suggests that multiple sclerosis represents a chronic stage of the same process which has been described here. Briefly, acute lesions of an "encephalomyelitic" type are common in multiple sclerosis, and transitional forms occur. In cases in which the course was typical for postmeasles "encephalitis" autopsy has shown the lesions of multiple sclerosis.[50] The experiments on animals which have already been mentioned may be taken as further evidence.

Reasons for believing that sclerotic plaques are the product of primary thrombosis have also been given elsewhere.[51] More recent

49. Putnam, T. J.: Studies in Multiple Sclerosis: VII. Similarities Between Some Forms of "Encephalomyelitis" and Multiple Sclerosis, Arch. Neurol. & Psychiat. **35**:1289-1308 (June) 1936.

50. Cramer, A.: Beginnende multiple Sklerose und acute Myelitis, Arch. f. Psychiat. **19**:667-683, 1888. Schlesinger, H.: Zur Frage des akuten multiplen Sklerose und des Encephalomyelitis disseminata im Kindesalter, Arb. a. d. neurol. Inst. a. d. Wien. Univ. **17**:410-434, 1909.

51. Putnam, T. J., and Adler, A.: Vascular Architecture of the Lesions of Multiple Sclerosis, Arch. Neurol. & Psychiat. **38**:1-15 (July) 1937. Putnam (footnotes 20 and 46).

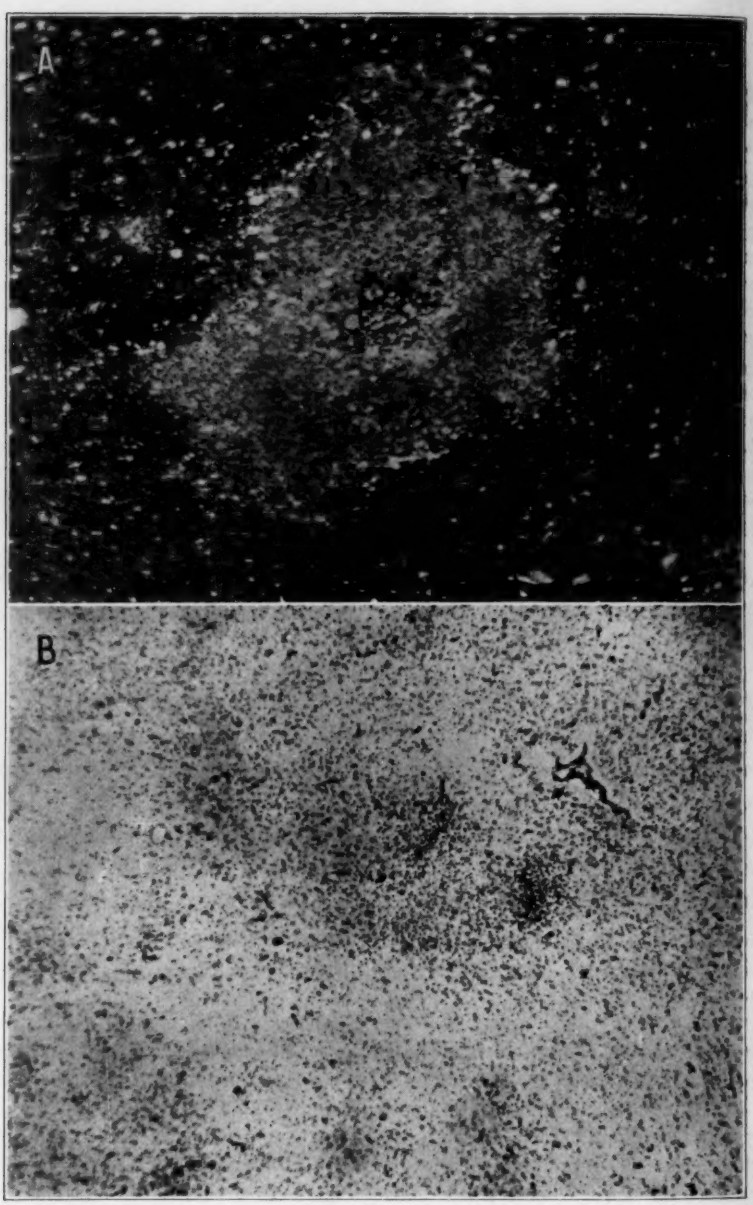

Fig. 10.—*A*, area of demyelination, and *B*, diffuse glial proliferation in the same region in adjacent sections from the same block, in a case of "encephalitis" of unknown cause. Modified Weigert and gallocyanine stains; 16 mm. lens.

evidence on this point has been furnished by Alexander and Myerson,[52] who showed that sclerotic plaques closely resemble infarcted areas in specimens subjected to microincineration. Still more recently, Alexander and Myerson [53] showed that sclerotic plaques examined by a spectroscopic method show an iron content equaled only by areas of encephalomalacia, and unlike those of any known infectious process. A striking case of "acute multiple sclerosis" with vascular obstruction has been reported by Riser and Geraud.[54]

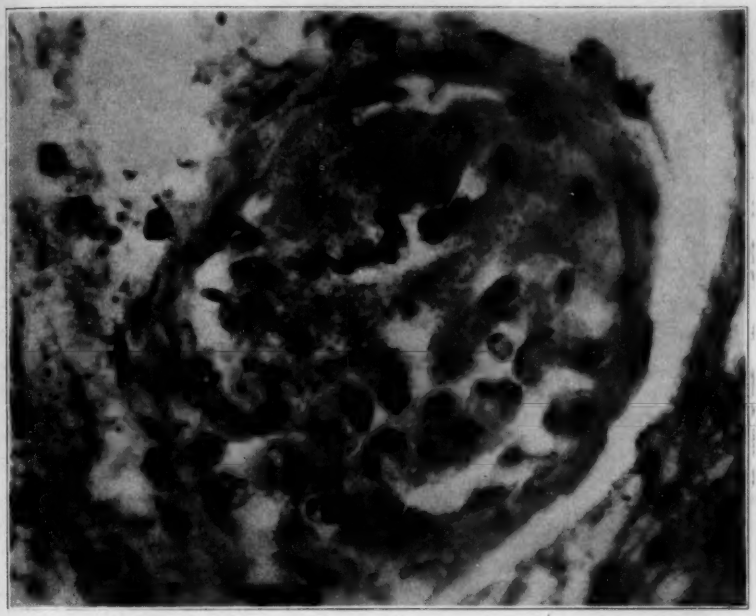

Fig. 11.—Organizing thrombus in a necrotic cerebral vessel, in the case of "encephalitis" illustrated in figure 10. Masson stain; oil immersion lens.

DIFFUSE SCLEROSIS AND "PERIAXIAL ENCEPHALITIS"

The miscellaneous group of diseases characterized by massive destruction of white matter have in the chronic stage certain similarities to

52. Alexander, L., and Myerson, A.: Mineral Content of Various Cerebral Lesions as Demonstrated by the Microincineration Method, Am. J. Path. **13**:405-440, 1937.

53. Alexander, L., and Myerson, A.: Minerals in Normal and in Pathologic Brain Tissue, Studied by Microincineration and Spectroscopy, Arch. Neurol. & Psychiat. **39**:131-149 (Jan.) 1938.

54. Riser and Geraud: Nouvelle observation anatomo-clinique de sclérose en plaques aiguë, Rev. neurol. **69**:348-361, 1938.

multiple sclerosis [55] and in the acute stage many resemblances to the acute "encephalitides." Bouman,[56] in a review of the literature, reported many cases of thrombosis, congestion and deposit of hematogenous pigment.

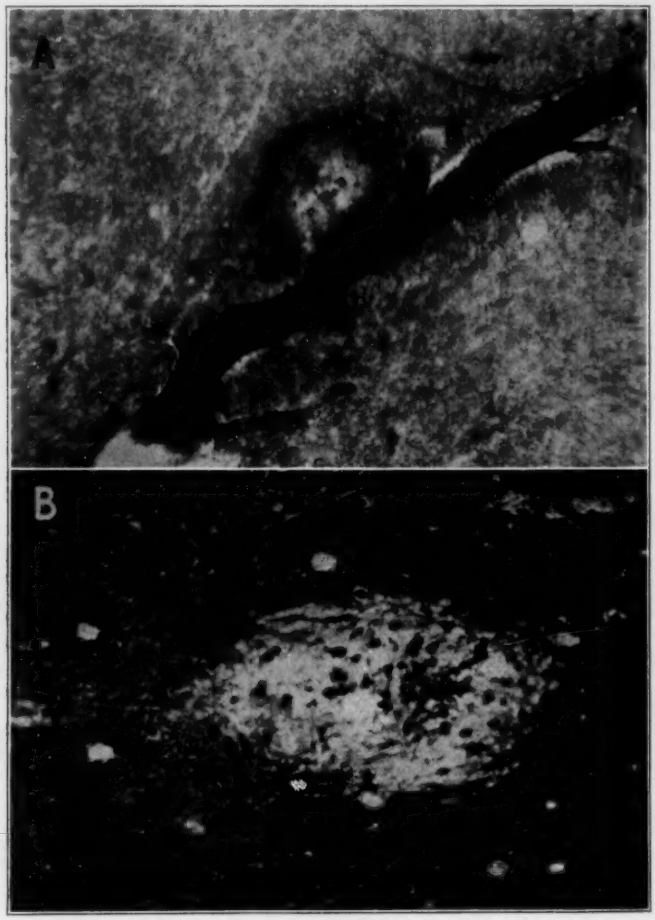

Fig. 12.—*A,* round area of demyelination, adjacent to a distended thrombosed vein, in a case of "encephalitis" in which the clinical course resembled that of von Economo's type. Masson stain; 16 mm. lens. *B,* demyelination and gliosis in the same case of "encephalitis" as that in which *A* was taken. Masson stain; 8 mm. lens.

55. Wertham, F.: Small Foci of Demyelinization in the Cortex and Spinal Cord in Diffuse Sclerosis: Their Similarity to Those of Disseminated Sclerosis and Dementia Paralytica, Arch. Neurol. & Psychiat. **27**:1380-1401 (June) 1932.

56. Bouman, L.: Diffuse Sclerosis: Encephalitis Periaxialis Diffusa, Baltimore, William Wood & Company, 1934.

In 4 cases available for study, there was considerable variation in the histologic picture. Sometimes the white matter alone, sometimes also the gray matter, showed widespread destruction, which spared axis-cylinders and glia slightly more than myelin and cell bodies. There were little progressive glial change and only moderate perivascular infiltration.

Evidences of vascular closure were observed in all cases examined. In the affected white matter it was often difficult to find vessels which contained blood, and often a fibrous cord was all that was left. Congestion and perivascular accumulation of pigment were common. Fresh thrombi were occasionally seen. They consisted of dense congeries of platelets in a fibrin framework or of masses of fibrin distending the vessel (fig. 13).

OTHER "DISSEMINATED ENCEPHALOMYELITIDES"

The group of diseases under discussion is ill defined. Many cases are recorded in the literature in which certain histologic similarities were

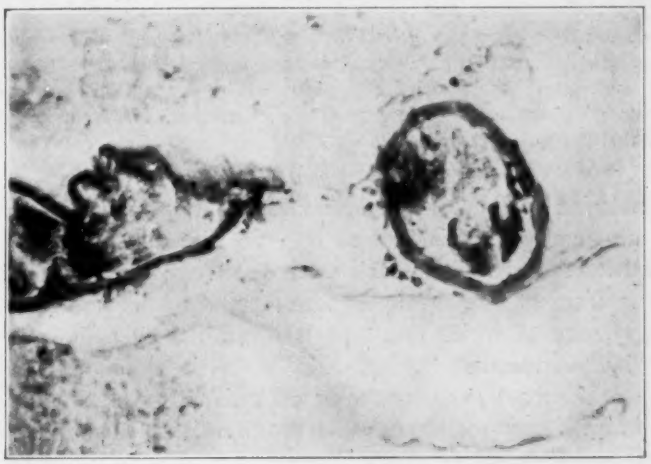

Fig. 13.—Masses of fibrin and débris distending a tortuous vessel, in a case of diffuse sclerosis. Mallory's connective tissue stain; 8 mm. lens.

shown (as has been pointed out by Marburg [3] and Ferraro,[4]) but whether or not they should be included in this group is at present a matter for speculation. One variation of the "encephalomyelitic reaction" deserves mention here: the concentric demyelination described by Baló [57] and others in cases of multiple and diffuse sclerosis. A suggestively similar form of degeneration has been observed by Alexander, Campbell and Putnam [24] in vascular foci. It is probably to be explained by the fact that vessels dilate around an infarcted area; if an extension of the thrombosis occurs, the marginal rim remains relatively well nourished, but degeneration may occur just beyond it.

57. Baló, J.: Encephalitis Periaxialis Concentrica, Arch. Neurol. & Psychiat. **19**:242-264 (Feb.) 1928.

Certainly, the explanation that the alternating zones are actually formed, like "Liesegang's rings," by diffusion of a noxious agent from a central point must appear naive to any one who has a dynamic conception of the capillary circulation of the nervous system.

"MYELITIS" AND MYELOMALACIA

The transverse lesions of the spinal cord of sudden onset and obscure origin have long been recognized, but are on the whole poorly understood. Infection, trauma and treatment by serums have appeared to be etiologic factors in some instances. The "myelitis" associated with optic neuritis (Devic's disease) bears some similarities to "disseminated encephalomyelitis" and to multiple sclerosis.[58] Bastian [59] reported seeing thrombi in "myelitic" lesions and considered them the primary cause. His cases were few, however, and the histologic report is inadequate.

In 1 case in the laboratory collection, a leukocytic thrombus was observed in the lesion. In 2 other cases of an older stage the lesion consisted of a cyst of softening such as is characteristically produced by arterial disease, with little "inflammatory" phenomena. There is reason, therefore, for including the condition in this group.

COMMENT

Formulation of the concept of nonsuppurative inflammation in the central nervous system is admitted to be difficult by all who have attempted it. Some authors, such as Pette,[60] have expressed the belief that virus diseases as a group produce pathognomonic lesions in the nervous system, of which one type is illustrated by poliomyelitis and another by postvaccinal "encephalitis." Hassin [61] suggested that an excessive widespread perivascular or parenchymatous exudate is diagnostic of an infectious disease, while proliferative changes in the walls of vessels and accumulation of phagocytes are ordinarily due to degenerative or toxic disease. Spielmeyer,[25] on the other hand, in a masterly article, has produced evidence to show that the histologic appearance of "encephalomyelitic" lesions gives little clue to their primary cause. Globus [6] made the following practical suggestion:

Useful as it is, the distinction between the inflammatory disease and its main anatomic landmark—the inflammatory reaction—is often not very clear, and a

58. Cestan, Riser and Planques: De la neuro-myélite optique, Rev. neurol. **2**:741-762, 1934.

59. Bastian, A.: Observations on Thrombotic Softening of the Spinal Cord as the Cause of So-Called "Acute Myelitis," Lancet **2**:1298-1321, 1937.

60. Pette, H.: Infektion und Nervensystem, Deutsche Ztschr. f. Nervenh. **110**: 221-290, 1929.

61. Hassin, G.: The Contrast Between the Brain Lesions Caused by Lead and Other Inorganic Poisons and Those Caused by Epidemic Encephalitis, Arch. Neurol. & Psychiat. **6**:268-286 (Sept.) 1921.

decision may be reached only when the provocative agent is identified and the existence of an infectious process is established, or when the finding of a noninfectious cause, such as a necrobiotic process due to vascular disturbances or provoked by a neoplasm, excludes the existence of an infectious agent and establishes the secondary or reactive character of the alterations.

All these authors have tacitly assumed that the postinfectious "encephalomyelitides" (to confine the discussion to these forms, for the sake of clarity) are the direct result of the activity of an infectious agent in the central nervous system.

Interpretation of proliferative and exudative phenomena of the "encephalomyelitic" type might be greatly simplified if a common factor could be found in all the conditions in which they occur. The function of the present paper is to point out that local interference with nutrition of tissues, in most instances local vascular obstruction, is adequate to cause such "inflammatory" phenomena and, as a matter of fact, can almost always be demonstrated by appropriate technic in lesions at the proper stage.

What are the causes of such thrombi?—for it is obvious that there must be many. In some forms, as in the "chronic subcortical encephalitis" of Binswanger,[18] the obstruction is due to endarteritis or endophlebitis. In others (for example, carbon monoxide and nitrogen monoxide poisoning), thrombi may be produced by asphyxia, as in the experiments of Stuber and Lang.[62] The situation is sufficiently clear also when the thrombus is propagated from a suppurative focus, as in meningitis and abscess. The fact that similar "encephalomyelitides" may be provoked in animals by the injection of organ extracts and bacterial products furnishes a possible explanation for the postinfectious types. Some thrombi may be of "allergic" origin (Dietrich and Schröder,[63] Alexander and Campbell [64]). A great group remains, however, in regard to which there is no precise information.

Obviously, such a point of view does not eliminate the possibility that thrombi, and hence the "encephalomyelitic reaction," may be due to a local infectious process. The histologic process cannot, however, be considered a proof of the existence of an infection. Evidence must be sought in other directions, for example, by fulfilling Koch's postulates.

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62. Stuber, B., and Lang, K.: Die Physiologie und Pathologie der Blutgerinnung, Berlin, Urban & Schwarzenberg, 1930.

63. Dietrich, A., and Schröder, K.: Abstimmung des Gefässendothels als Grundlage der Thrombenbildung, Virchows Arch. f. path. Anat. **274**:425-451, 1930.

64. Alexander, L., and Campbell, A. C. P.: Local Anaphylactic Lesions of the Brain in Guinea Pigs, Am. J. Path. **13**:229-248, 1937.

SUMMARY

1. The "encephalomyelitic reaction" may be defined as one consisting of a perivascular intra-adventitial and extra-adventitial accumulation of histiocytic and hematogenous cells, some of them phagocytic, with local degeneration of myelin sheaths (or of nerve cells) and local disseminated or diffuse glial proliferation, but without cyst formation or actual suppuration.

2. Such a process occurs in conjunction with many types of disease of the nervous system. It is, however, more typical and widespread in the group of diseases known as "disseminated encephalomyelitis" than in any other.

3. In the early stages of the reaction, congestion and thrombosis of vessels may be observed with considerable regularity. The appearance of these thrombi in various types of "encephalomyelitis" is described and illustrated.

4. Since evidences of vascular occlusion are so common in relation to the "encephalomyelitic reaction," since it is difficult to find instances of similar types of vascular occlusion without it and since it may be produced experimentally by appropriate interference with the blood supply of the brain, it seems reasonable to conclude that the vascular occlusion is primary to the histologic changes.

5. The possible origins of such thrombi are discussed.

INFLUENCE OF THE BLOOD SUGAR LEVEL ON THE WAVE AND SPIKE FORMATION IN PETIT MAL EPILEPSY

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E. L. GIBBS

AND

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Since the beginning of our work on the electrical activity of the cortex,[1] we have attempted to distinguish between the different types of abnormal waves that are encountered in epilepsy. We have described the wave and spike of petit mal,[2] the crescendo burst of fast waves of grand mal [2] and the slow square waves and high voltage 6 per second waves of psychic equivalent seizures.[3]

Characteristic examples of these various formations have been published,[2d] but for ease of reference they are shown again in figure 1. It will be noted that there are two kinds of wave and spike activity: (1) the approximately 3 per second wave and spike rhythm of the true

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From the Department of Neurology, Harvard Medical School, and the Neurological Unit, Boston City Hospital.

1. Gibbs, F. A.; Davis, H., and Lennox, W. G.: The Electro-Encephalogram in Epilepsy and in Conditions of Impaired Consciousness, Arch. Neurol. & Psychiat. **34**:1133 (Dec.) 1935.

2. (*a*) Gibbs, F. A.; Lennox, W. G., and Gibbs, E. L.: The Electro-Encephalogram in Diagnosis and in Localization of Epileptic Seizures, Arch. Neurol. & Psychiat. **36**:1225 (Dec.) 1936. (*b*) Gibbs, F. A.; Gibbs, E. L., and Lennox, W. G.: Cerebral Dysrhythmias of Epilepsy: Measures for Their Control, ibid. **39**:298 (Feb.) 1938; (*c*) Epilepsy: A Paroxysmal Cerebral Dysrhythmia, Brain **60**:377 (Dec.) 1937. (*d*) Gibbs, F. A.: The Electro-Encephalogram in Epileptic Seizures, in Oppenheimer, C., and Pincussen, L.: Tabulae biologicae, The Hague, U. Junk, 1938, vol. 16, no. 2, p. 128. (*e*) Gibbs, Davis and Lennox.[1]

3. (*a*) Gibbs, F. A.; Gibbs, E. L., and Lennox, W. G.: The Likeness of the Cortical Dysrhythmias of Schizophrenia and Psychomotor Epilepsy, Am. J. Psychiat. **95**:255 (Sept.) 1938; (*b*) footnotes 2 *b* and *c*. (*c*) Lennox, W. G.; Gibbs, F. A., and Gibbs, E. L.: Effect on the Electro-Encephalogram of Drugs and Conditions Which Influence Seizures, Arch. Neurol. & Psychiat. **36**:1236 (Dec.) 1936. Gibbs.[2d]

petit mal seizure which is commonly accompanied by clonic muscle jerks, synchronous with the 3 per second rhythm, and (2) the slow wave and spike formation which repeats approximately twice a second and is associated with a type of seizure which we have called "petit mal variant." In this form of attack there is usually no clonic movement, and the impairment of consciousness is less complete than in the typical petit mal seizure with the 3 per second rhythm.

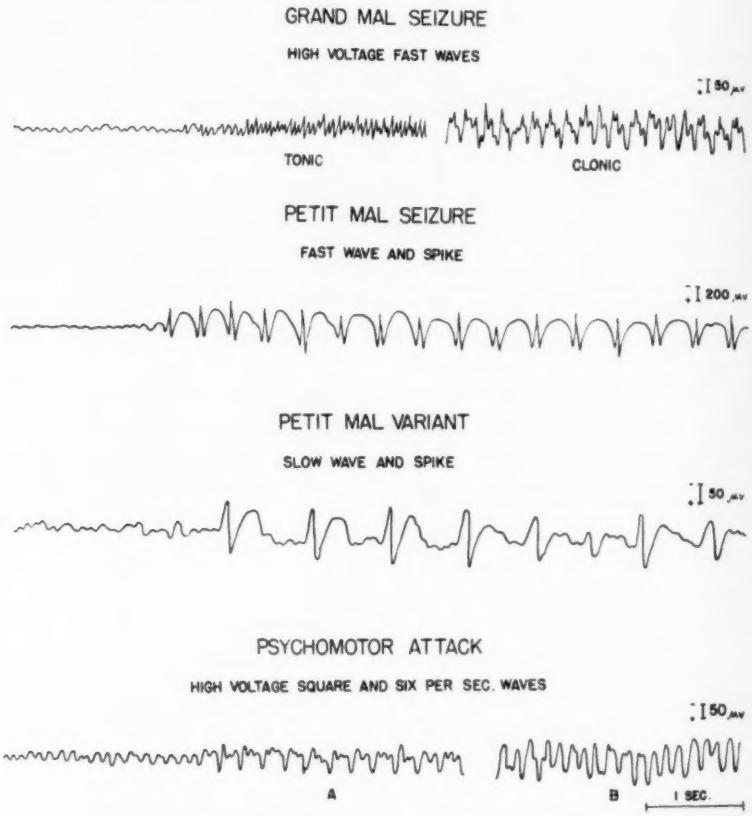

Fig. 1.—Types of abnormal activity encountered in epilepsy and the variety of seizure with which each is associated (from an article by one of us [F. A. G.]).[2d] *Grand Mal Seizure:* Typical pattern, with electrodes on the left frontal region and ear. *Petit Mal Seizure:* Typical pattern, with electrodes on the left frontal region and ear. *Petit Mal Variant:* Typical pattern, with electrodes on the left occipital region and ear. *Psychomotor Attack:* Typical pattern, with electrodes on the left occipital region and ear. *A* represents the onset; *B*, a later phase. These abnormal patterns can appear without, as well as with, clinically obvious seizures.

Isolated foci of 3 per second wave and spike activity are most commonly found in the frontal and the precentral area. From these areas, also, isolated bursts of fast activity of the grand mal type are most frequently obtained. Isolated foci of 2 per second wave and spike activity, on the other hand, occur most commonly in the postcentral and occipital areas, and here also isolated foci of square waves and high voltage 6 per second activity are most commonly encountered. We have previously suggested that there is a relationship between the fast waves of grand mal, the spike of the true petit mal seizure and the normal fast activity of the precentral and frontal regions. There appears also to be a relationship between the slow spike or hump of the petit mal variant, the 6 per second wave of the psychomotor seizure and the normal 10 per second wave of the postcentral and occipital areas. In this connection it is worth noting that several patients had slow wave and spike activity which could not be altered by varying the carbon dioxide tension of the blood or by changing the level of the blood sugar, but which dropped out immediately when the eyes were opened.

We do not claim that there is a sharp boundary between one form of abnormality and another. Mixtures of abnormal patterns are not uncommon, and transition forms are occasionally seen.

The differential action of various drugs and procedures on the abnormal rhythms of epilepsy has been reported in previous papers.[4] We wish now to report specifically on the differential action of blood dextrose, particularly its effect on the 3 per second wave and spike activity and its lack of effect on the 2 per second wave and spike of the petit mal variant.

Thirty-four patients with grand mal, petit mal or psychomotor (psychic equivalent) seizures were given large doses (from 60 to 100 units) of insulin followed by dextrose, and the changes produced in the electrical activity of the cortex as the blood sugar fell and rose were noted. The purpose was not to produce severe insulin shock, such as is used in the treatment of schizophrenia. Only on three or four occasions did patients become stuporous. Although in 2 of the cases the condition had been diagnosed elsewhere as epilepsy due to hypoglycemia, in no case was either a grand mal or a psychomotor seizure precipitated by the low sugar level. Generalized tonic-clonic convulsions are not easily induced by hypoglycemia in man. Of 600 insulin shocks induced in patients with schizophrenia, Vander Veer and Reese [5] observed this type of reaction in only 3 per cent. In none of our 16 patients with a history of grand mal seizures was there evidence of an increase in the

4. Gibbs, Gibbs and Lennox.[2b] Lennox, Gibbs and Gibbs.[3c]

5. Vander Veer, A. H., and Reese, H. H.: Treatment of Schizophrenia with Insulin Shock, Am. J. Psychiat. **95**:271 (Sept.) 1938.

grand mal type of activity. In none of the 10 patients with the petit mal variant type of seizure, i. e., the 2 per second wave and spike, was the abnormal activity significantly increased. On the other hand, in all (18) patients showing a 3 per second wave and spike, a tremendous increase in this type of abnormal activity occurred when the sugar level of the blood fell to 50 mg. per hundred cubic centimeters or below. Figure 2 shows the relation in a typical case between the blood sugar level and the amount of wave and spike activity. In the normal subject a blood sugar level of 50 mg. per hundred cubic centimeters is by no means low enough to produce abnormal waves. They appear when the level of sugar in the blood of the internal jugular veins falls to 30 mg. per hundred cubic centimeters or below. These abnormal waves in the nonepileptic subject do not, however, have the characteristic form of the 3 per second wave

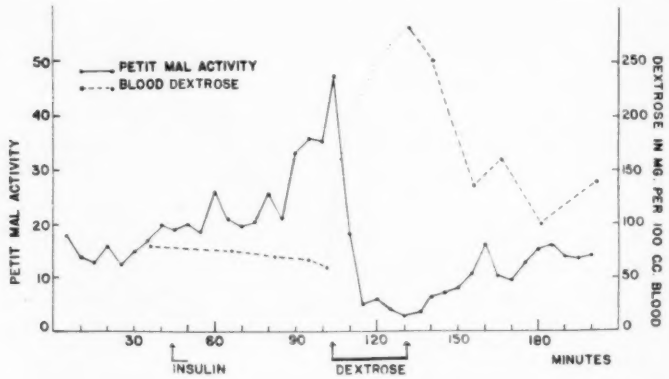

Fig. 2.—Relation of the amount of 3 per second wave and spike activity to the concentration of dextrose in the blood in patient C. G. The abscissa represents the number of minutes, and the left hand ordinate (and the solid line) indicate the percentage of each minute during which the 3 per second wave and spike activity was present. The right hand ordinate (and the line of dashes) represent the number of milligrams of dextrose per hundred cubic centimeters of blood from the finger tip (microdeterminations). The dotted line represents the period of injection of dextrose.

and spike; they are moderately high voltage irregular waves with frequencies below 8 per second. Thus, it appears that there is not a direct and simple etiologic relationship between a low level of the blood sugar and the 3 per second wave and spike. Hypoglycemia precipitates these waves only in patients having a special type of epilepsy.

When the blood sugar was raised well above normal levels by the injection or ingestion of dextrose, all patients with a 3 per second wave and spike showed a great reduction in the amount of this activity; other types of abnormal activity were not appreciably affected.

For several days following a period of hypoglycemia produced with insulin, patients with the 3 per second type of petit mal usually had less of this disorder and were improved clinically (fig. 3). A period of improvement, as judged by the electrical record, followed in 19 of 21 trials with the 8 patients who were studied after the hypoglycemia. This beneficial effect cannot be explained by the assumption that so many seizures occurred during the period of hypoglycemia that all seizures were "drained off," for the length of the remission was not proportional to the severity of the insulin reaction, to the number of insulin reactions or to the amount of wave and spike activity during the hypoglycemia. It is likewise impossible to ascribe the remission to a high level of the blood

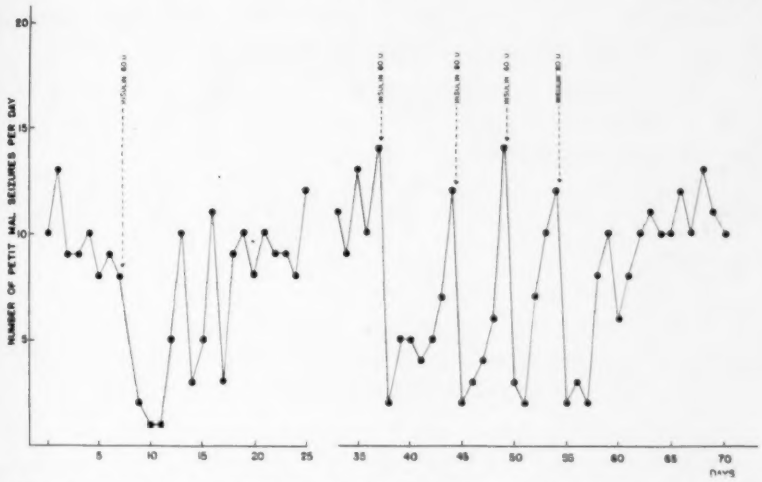

Fig. 3.—Effect of insulin hypoglycemia followed by administration of dextrose by mouth on the daily count of petit mal seizures of patient D. B. (Seizures during the period of hypoglycemia are not plotted.) As will be seen, the patient was relatively free from attacks for from three to four days after each insulin-dextrose treatment.

sugar on the days following the insulin reaction, for in the 4 patients observed the blood sugar level was not then elevated.

A differential action similar to the effect of dextrose is observable with carbon dioxide, for the 3 per second wave and spike formation is exceedingly sensitive to changes in the carbon dioxide tension of the blood,[2b] whereas the 2 per second wave and spike activity is not. In our experience, all 3 per second wave and spike disorders were greatly affected by changes in both sugar and carbon dioxide. On the other hand, 2 per second wave and spike formations were little, if at all, affected by either. It should be noted that not all patients with 3 per second wave and spike formations are equally sensitive to changes in the

sugar or the carbon dioxide level in the blood. Some patients will "blow up" with a relatively high level of the blood sugar and others only with a really low level. The same may be said for the carbon dioxide tension of the blood.

CONCLUSIONS

1. High blood sugar decreases and low blood sugar increases the 3 per second wave and spike activity of petit mal epilepsy.

2. In cases of this type of abnormality an insulin reaction may produce amelioration of petit mal, which lasts for from one to three days, or possibly longer.

3. On the other hand, a similar, but distinct type of abnormal activity—the 2 per second wave and spike of the petit mal variant—is not sensitive to variations in the level of sugar in the blood.

4. The abnormal electrical activity of the brain which is characteristic of grand mal epilepsy, namely, a crescendo burst of fast waves, is not sensitive to variations in blood sugar.

5. The abnormal activity which is characteristic of psychic epilepsy, namely, square waves and high voltage 6 per second waves, is insensitive to variations in the level of the blood sugar.

6. If an abnormal formation is affected by variations in the level of sugar in the blood, it will respond to variations in the carbon dioxide of the blood; if unaffected by variations in blood sugar, it will not respond to variations in the carbon dioxide tension of the blood.

ARM TO CAROTID CIRCULATION TIME IN ABNORMAL MENTAL STATES

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This communication is a report of the results of a study of the blood velocity, as determined by the sodium cyanide method of measuring the arm to carotid circulation time, in patients suffering from various abnormal mental states. The investigation was stimulated by the fact that the blood velocity had been reported previously by Freeman [1] as abnormally slow in patients with schizophrenia. If his results could be confirmed it would be an opening wedge in the study of the pathologic physiology of this disease. At a later date, however, Finesinger, Cohen and Thomson,[2] utilizing the same method, were unable to confirm Freeman's results and reported that the arm to carotid circulation time for patients suffering from schizophrenia was normal. Because of the marked discrepancy in these reports, the results of the present study are given. This investigation was not confined to a check of the preceding studies on schizophrenia; it included studies of the arm to carotid circulation time in other mental conditions. This was done with the purpose of comparing the values found in patients suffering from one mental disease with those of patients suffering from another to determine whether any mental disease is characterizied by an abnormality of this circulation time.

Freeman,[3] although consistently showing a more rapid arm to carotid circulation time for his normal subjects serving as controls than for his schizophrenic groups, reported different means for each series of observations. In the first series of 73 male patients with schizophrenia the mean circulation time was 25.6 seconds; in a second series of 52 patients the mean value was 27 seconds, and in a third

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From the Iowa State Psychopathic Hospital.

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1. Freeman, H.: The Arm-to-Carotid Circulation Time in Normal and Schizophrenic Subjects, Psychiatric Quart. **8**:290 (April) 1934.

2. Finesinger, J. E.; Cohen, M. E., and Thomson, K. J.: Velocity of Blood Flow in Schizophrenia, Arch. Neurol. & Psychiat. **39**:24 (Jan.) 1938.

3. Freeman, H.: (*a*) The Variability of Circulation Time in Normal and in Schizophrenic Subjects, Arch. Neurol. & Psychiat. **39**:488 (March) 1938; (*b*) footnote 1.

series [3a] of 32 patients the mean was 23.2 seconds. Likewise, for his normal controls there were variations: For 26 normal male subjects the mean circulation time was 21.9 seconds, and for the second series of 29 male subjects the mean value was 19.1 seconds.

The value obtained by Finesinger and his associates, that of a mean circulation time of 14.9 seconds for a group of 55 patients with schizophrenia, indicated a decidedly faster arm to carotid velocity of the blood than Freeman obtained for either his normal or his psychotic subjects. Finesinger used as comparable values for normal groups, those reported by Robb and Weiss,[4] Gargill [5] and Cohen and Thomson.[6] Their averages were 15.6, 15.6 and 15.7 seconds, respectively.

METHOD

In order to minimize the influence of extraneous factors, the determinations were performed early in the morning under strictly basal conditions. All patients entering the Iowa State Psychopathic Hospital were used as subjects, except those under 16 years of age, those having marked evidence of arteriosclerosis, those so disturbed as to be uncooperative and those showing organic disease not related to their psychosis. Both male and female patients were included. The circulation time for each patient was determined on the first Friday after admission. Collection of the data required over six months. The seasonal variation, however, had no effect on the circulation time.

The technic of the test, as described by Robb and Weiss,[4] is simple. After the fluctuations of the circulatory mechanisms were reduced to a minimum, as noted by constancy in determinations of the pulse rate, 10 mg. of sodium cyanide in a 2 per cent aqueous solution was drawn into a small syringe. The median basilic vein in the right arm was punctured; the tourniquet was released, and after an interval of sixty seconds to overcome venous stasis the solution was rapidly injected. The end point of the reaction was marked by a sudden onset of transitory hyperpnea and tachycardia, due, presumably, to arrival of the cyanide at the carotid sinus. The interval of time between the injection of the drug and the first sharp respiratory gasp was measured by a stopwatch. This was taken as the arm to carotid circulation time. If a sharp end point was not obtained the test was repeated ten minutes later, 12 mg., or 0.6 cc. of a 2 per cent solution, being employed. In no case did the latter dose fail to give the desired respiratory effect.

Although the technic as described is simple, it varied from that employed by Freeman and Finesinger, which may account for some of the differences in the results of these two investigators. Freeman

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4. Robb, G. P., and Weiss, S.: A Method for the Measurement of the Velocity of the Pulmonary and Peripheral Venous Blood Flow in Man, Am. Heart J. **8**: 650 (June) 1933.

5. Gargill, S. L.: The Use of Sodium Dehydrocholate as a Clinical Test of the Velocity of Blood Flow, New England J. Med. **209**:1089 (Nov. 30) 1933.

6. Cohen, M. E., and Thomson, K. J.: Studies on the Circulation in Pregnancy: Velocity of Blood Flow and Related Aspects of Circulation in Normal Pregnant Women, J. Clin. Investigation **15**:607 (Nov.) 1936.

employed a dosage of 10 mg. of sodium cyanide as his optimal dose, repeating the injection with a larger amount only when he failed to obtain a sharp end point. Finesinger determined his optimal dosage by repeating the injection at five minute intervals, beginning with a very small dose and increasing the amount by 2 or 3 mg. at each injection. He reached his optimal dose when the amount was sufficient to give on repetition a value for the arm to carotid circulation time within 2 seconds. His optimal dose of sodium cyanide averaged 6.8 mg., the maximum amount being 9.2 mg.

Finesinger, citing Weiss, reported that the first dose of sodium cyanide administered required a longer time to produce the respiratory response than did the same amount of the drug in subsequent doses. He suggested that this may be due to sensitization of the carotid sinus mechanism by the first dose. It is surprising that the disturbance of the basality of the subject's cardiovascular system by the first injection was not considered as a factor. With an increased circulation rate, if not allowed to return completely to a basal state, a repeated test would be expected to give a faster circulation time. On an average, this may account for a discrepancy of 2 or 3 seconds. Finesinger's rates would have been slower and Freeman's faster if their technic had been different.

In this study the technic employed was that described by Freeman, for it is his results which are most provocative.

RESULTS AND COMMENT

A total of 150 patients were submitted to the procedure described. Seventy-two were males, and 78 were females. The mean age was 32.11 years. All were free from demonstrable organic disease other than that related to the illness. The circulation time for the group varied from a minimum of 9.7 to a maximum of 47.8 seconds, thus demonstrating the pronounced variation that can be obtained in different persons. The mean circulation time for the group was 18.01 seconds. In the distribution the skew was to the left.

The individual values were then first considered as all belonging to one population, and the circulation time was correlated with a number of variables. There existed a low coefficient of correlation with a pulse rate of -0.343 ± 0.05. This means that the slower the pulse rate the slower the rate of blood flow. Other measurable descriptive variables, such as age, height, weight and length of illness, showed no relationship.

In correlating physiologic variables, such as slight arteriosclerosis, permeability quotient of the spinal fluid bromides, spinal fluid protein, blood sugar and blood nonprotein nitrogen with the arm to carotid circulation time, only the values for arteriosclerosis indicated a relationship.

In the entire group there were 11 patients with slight vascular changes. Their mean circulation time was 24.4 seconds, a statistically significant increase from the mean value of 18.01 seconds for the entire group. Thus, arteriosclerosis, even when slight, seems to cause slowing of the rate of blood flow.

The measured psychologic variables, such as degree of tension, amount of psychomotor activity and contact with environment, showed, interestingly, no relationship with the circulation time.

In table 1 are summarized the mean arm to carotid circulation times obtained for the patients suffering from the various diseases. The mean circulation time for the group of 29 schizophrenic patients was 17.76 seconds. The range was from 13 to 27.7 seconds—considerably less than the range of from 12 to 40 seconds reported by Freeman, but comparable with the range of from 11 to 26 seconds obtained by Finesinger. Of all the data measured (table 3), only the pulse rate showed any tendency to relationship with the circulation time, as indicated by the correlation coefficient of -0.445 ± 0.10 (0.47).[7] This means that the slower the pulse rate the longer the arm to carotid circulation time. Thus, the value obtained will be dependent in part on the degree of basality of the subject.

Examination of the constants obtained for other disease groups showed that schizophrenia is not characterized by slowing of the blood velocity. As can be noted in table 1, the groups of psychoneurotic patients and those with psychopathic personalities had mean arm to carotid circulation times of 17.21 and 18.05 seconds, respectively. These are not significantly different from the value obtained for the schizophrenic group (table 2). Likewise, the means for the following variables—pulse rate, age, height, weight, permeability quotient of spinal fluid bromides, spinal fluid protein, blood sugar and blood nonprotein nitrogen—did not differ significantly for the three groups (table 3). Neither were there any significant correlations of these variables with the circulation time, except for the pulse rate.

For the 20 patients having a condition diagnosed as psychopathic personality without psychosis the range varied from a minimum of 10 to a maximum of 29.6 seconds. The values obtained for this group can be considered as normal, for no diseases were superimposed on the constitutional deficiency. As with the schizophrenic group, the only significant coefficient of correlation was that with the pulse rate -0.634 ± 0.09 (0.65).

The range of the circulation time for the psychoneurotic group was equally broad, extending from a minimum of 10.3 to a maximum of

7. The correlations were computed by the method of rank differences. The figures in parentheses indicate corrections for r.

TABLE 1.—*Constants of Distributions of the Circulation Time for the Various Diseases and for Sex*

Diagnosis	Total Group					Males				Females				Differences Between Males and Females	
				Standard Deviation of				Standard Deviation of				Standard Deviation of			
	No.	Range	Mean	Mean	Distribution	No.	Mean	Mean	Distribution	No.	Mean	Mean	Distribution	Critical Ratio*	P†
Total groups	150	9.7-47.8	18.01	.....	....	72	18.92	....	....	78	17.16	.....	....	....	..
Manic-depressive psychosis	37	12.3-47.8	19.80	.....	....	18	21.17	....	....	19	18.50	.....	....	....	..
Depressions	26	12.3-47.8	19.80	1.275	7.50	14	21.61	2.28	8.53	12	17.70	1.570	5.44	1.40	92
Manic attacks	11	13.2-26.8	19.79	1.454	4.82	4	19.62	1.96	3.91	7	19.88	2.000	5.29	....	..
Involutional melancholia	10	12.7-30.8	19.94	1.493	5.72	2	24.20	....	....	8	18.87	1.736	4.91	....	..
Schizophrenia	29	13.0-27.7	17.76	0.726	3.91	10	19.12	1.75	5.53	19	17.04	0.571	2.49	1.13	87
Psychopathic personality	20	10.0-29.6	18.05	1.115	4.99	10	19.70	1.74	5.52	10	16.41	1.100	3.97	1.60	94
Psychoneurosis	30	10.3-29.4	17.21	0.856	4.69	19	18.19	1.19	5.22	11	15.50	0.870	2.89	1.82	96
Psychopathic personality with psychosis	5	13.0-31.4	17.74	.....	....	..	.....	....	....	5	17.74	.....	....	....	..
Toxic and organic psychosis	19	9.7-20.8	15.15	0.638	2.78	13	15.30	0.89	3.19	6	14.80	0.932	2.28	....	..

* Critical ratio $= \frac{\text{Obtained difference}}{\text{Standard deviation difference.}}$

† P indicates chances in 100 (over 90 is significant).

TABLE 2.—*Reliability of Differences Between the Means for the Disease Syndromes*

	Depressions		Manic Attacks		Involutional Melancholia		Schizophrenia		Psychopathic Personality		Psychoneurosis		Toxic and Organic Psychoses	
	Critical Ratio*	P†	Critical Ratio	P	Critical Ratio	P	Critical Ratio	P	Critical Ratio	P	Critical Ratio	P	Critical Ratio	P
Depressions	....	..	0.00	0	0.07	53	1.32	90	1.59	94	1.68	96	3.25	100
Manic attacks	0.00	0	....	..	0.07	53	1.25	89	0.95	83	1.53	93	3.00	100
Involutional melancholia	0.07	53	0.07	53	....	..	1.31	90	1.02	84	1.59	94	2.96	99
Schizophrenia	1.32	90	1.25	89	1.31	90	....	..	0.22	58	0.49	69	2.68	99
Psychopathic personality	1.59	94	0.95	83	1.02	84	0.22	58	....	..	0.60	73	2.25	99
Psychoneurosis	1.68	96	1.53	93	1.59	94	0.49	69	0.60	73	....	..	1.93	97
Toxic and organic psychoses	3.25	100	3.00	100	2.96	99	2.68	99	2.25	99	1.93	97	....	..

* Critical ratio $= \frac{\text{Obtained difference}}{\text{Standard deviation difference.}}$

† P indicates chances in 100 (over 90 is significant).

TABLE 3.—*Means for the Measured Variables*

Diagnosis	Number	Circulation Time, Sec.	Pulse Rate, per Min.	Age, Years	Height, Inches	Weight, Lb.	Length of Illness, Mo.	Permeability Quotient	Spinal Fluid Protein, Mg.	Blood Sugar, Mg.	Blood Nonprotein Nitrogen, Mg.
Total groups	150	18.01	75.91	32.11	65.65	134.54	16.83	2.81	37.51	88.13	37.29
Manic depressive psychosis	37	19.80	74.54	33.80	66.00	137.00	4.03	2.77	39.77	87.51	36.52
Depressions	26	19.80	76.38	36.23	65.64	138.30	5.08	2.70	42.91	87.00	36.73
Manic attacks	11	19.79	70.20	28.00	66.50	134.00	1.55	2.95	29.98	88.75	36.00
Involutional melancholia	10	19.94	73.40	51.10	61.60	123.80	8.50	2.48	40.00	90.64	38.26
Schizophrenia	29	17.76	76.93	27.60	65.07	129.20	11.00	2.94	34.44	91.67	38.26
Psychopathic personality	20	18.05	72.25	28.65	65.95	137.40	Life	2.86	34.46	86.30	37.97
Psychoneurosis	30	17.21	78.13	29.30	66.43	134.00	30.40	2.98	37.00	86.61	37.56
Psychopathic personality with psychosis	5	17.74	66.40	27.60	64.40	132.20	47.40	2.78	29.98	87.84	34.20
Toxic and organic psychosis	19	15.15	81.16	35.00	67.20	137.00	25.60	2.56	42.32	87.27	36.02

29.4 seconds. The coefficient of correlation with the pulse rate was -0.174 ± 0.13 (0.18) and was of no significance. The reason for this is not clear. Perhaps it is a reflection of the emotional instability of the psychoneurotic patient in his reaction to a test situation.

Therefore, because there were no significant differences in the three groups, it seems justifiable to conclude that schizophrenia is not characterized by an abnormality of the rate of blood flow.

COMMENT

The mean value for schizophrenia reported here confirms that obtained by Finesinger. The difference of about 2.5 seconds between the mean he obtained and that reported here is not significant and is probably due to variation in the respective technics.

This raises the question why the values reported by Freeman for his psychotic subjects were slower than those obtained in this investigation. The discrepancy, however, is not as pronounced as appears at first sight, since a number of factors enter which tend to bring the two groups of data together. What appears to be of primary importance is the relative degree of basality of the subjects at the time of injection of the sodium cyanide. Freeman's patients were habituated to test situations. Most of them had been hospitalized for considerable periods (years) and were in a relatively well advanced, chronic, deteriorated schizophrenic state. Moreover, they had become accustomed to test procedures, for they were repeatedly being used as experimental subjects. In contrast, the schizophrenic patients used in this study were in an acute phase of the disease and showed relatively slight evidences of deterioration. The average duration of the disease process was eleven months. In addition, the test situation was thrust on the patients even before they had adjusted to the hospital situation. As a result, varying degrees of apprehension were present in all these patients. A reflection of the basal state is furnished by the pulse rate. The mean pulse rate in Freeman's series was 61 per minute; in Finesinger's series, 82 per minute, and in the series reported here, 77 per minute. It has already been shown that there is a relationship between pulse rate and blood velocity—the slower the pulse rate the longer the circulation time. The differences in the basal conditions under which the tests were performed, therefore, probably account for some of the discrepancy between the results of Freeman's test and the results reported here.

Another factor which is of importance in interpreting this discrepancy is that of sex. All of Freeman's subjects were males. The data here reported were obtained on both males and females. In table 1 it can be seen that the means for the groups of female patients with each disease, except the manic group, which is small, were lower than

those for the male patients. Although the individual groups are so small that they cannot be relied on for statistical purposes, the general consistency indicates a probable reliability in considering sex as a factor in the blood velocity. Since the schizophrenic group reported here was partially composed of women, it follows that the mean circulation time was faster than if the group had been composed entirely of men. However, the mean circulation time for the male schizophrenic group was 19.1 seconds, still considerably faster than the fastest mean circulation time of 23.2 seconds reported by Freeman.

One of the slower mean rates of blood flow, that of 19.8 seconds, was found for the group of 37 patients with manic-depressive psychosis. The range, however, was broad, extending from a minimum of 12.3 to a maximum of 47.8 seconds. The distribution was skewed to the left, as indicated by the second longest circulation time, that of 33.8 seconds. The mean for the depressed patients was the same as the mean for those in a manic attack. These mean values were suggestive of being statistically significant slower rates than those obtained for the groups of patients with schizophrenia, psychopathic personality and psychoneurosis, and were definitely so for the group of toxic and organic psychoses (table 2). The only other group of patients that had a comparable slow rate of blood flow was that with involutional melancholia (table 2).

None of the measured variables, including the pulse rate, showed any definite relationship with the circulation time. For the group of 26 depressed patients the coefficient of correlation with the pulse rate was -0.341 ± 0.12 (0.35), and that for the 11 manic patients, -0.252 ± 0.20 (0.26). Since these values are less than four times their probable errors, they have no significance. Of importance, however, was the fact that neither the intense psychomotor activity of the manic patient nor the deep stupor of the depressed patient seemed to have any effect on the rate of blood flow. Likewise, the tenseness of the patient could not be discerned as influencing this variable. This is in contrast to what one would expect from the normal subject, in whom under tension or increased activity the velocity of the blood increases to assist in the disposal of the metabolites and thus help maintain what Cannon so aptly designated "the constancy of the internal milieu."

Further evidence suggestive of abnormality of the rate of blood flow in patients with a manic-depressive psychosis is shown by examining the means obtained for the various attacks of the disease. The 20 patients in a first attack had a mean circulation time of 17.24 seconds; the 9 in a second attack, 22.06 seconds, and the 8 in a third attack, 23.65 seconds. This progressive increase is probably significant. It indicates possibly an increasing abnormality of the circulatory system with progression of the disease.

The mean circulation time for the 10 patients suffering from involutional melancholia was 19.94 seconds—practically the same as that for the manic-depressive group. Likewise, the range was large, varying from a minimum of 12.7 to a maximum of 30.8 seconds. This rate of blood flow closely approached being significantly slower than the blood velocity for all the other disease syndromes except the manic-depressive psychosis (table 2). In searching for an explanation of this decrease in the blood flow in the group with involutional melancholia, several factors seem to be of importance. The mean age, 51.1 years (table 3), was considerably greater than that of 33.8 years obtained for the manic-depressive patients. The mean permeability quotient (table 3) for the patients with involutional melancholia was 2.48, significantly lower than the mean of 2.77 for the manic-depressive group. This probably indicates slight vascular involvement in the patients with an involuntional psychosis. It already has been shown that arteriosclerosis causes an increase in the circulation time, or a decrease in the rate of flow. Since the age in this group was consistent with beginning vascular pathologic changes, it seemed that this factor must be considered as important in explaining the slow blood velocity. Except for these, all the variables measured showed no significant differences in means or correlations between the groups of patients with manic-depressive psychosis and those in the involutional state.

In the last group, composed of patients with toxic psychoses and psychoses associated with organic disease of the brain, the mean circulation time for the 19 patients was 15.15 seconds. This is a significantly faster rate of blood flow than that found for any other group. Even the group variability was the least, ranging from a minimum of 9.7 to a maximum of 20.8 seconds. Of course, one would expect a toxic state to cause the organism to react by mobilization of its protective forces and the blood velocity thereby to increase. Of interest here, however, is the fact that the severity of the psychotic symptoms seemed to have no relation to the rate of blood flow. Furthermore, as in the other groups, all attempts to establish correlations between the circulation time and the other measured variables, even the pulse rate, failed. This correlation coefficient of -0.362 ± 0.14 (0.37) was low and was not significant. It seems, therefore, that although an increase of the blood velocity is associated with the various toxic and organic psychoses, the important element is the toxicity rather than the intensity of the mental symptoms.

SUMMARY

The arm to carotid circulation time was studied under basal conditions in 150 patients with various mental diseases; 72 were males and 78 females. The mean circulation time was 18.01 seconds. The range

was from a minimum of 9.7 to a maximum of 47.8 seconds. The mean circulation time for 11 patients with slight arteriosclerosis was 24.4 seconds, which was highly suggestive of significant slowing of the rate of blood flow.

The mean circulation time for the 29 schizophrenic patients was 17.76 seconds, with a range from 13 to 27.7 seconds. This did not differ significantly from the mean circulation times of 17.21 seconds for the 20 patients with psychoneurosis and 18.05 seconds for the 20 patients with psychopathic personality. These values were considered within the normal range.

The mean circulation time for the 37 patients with manic-depressive psychosis was 19.8 seconds, which was highly suggestive of a statistically significant slower rate of blood flow than that obtained for any other group except that with involutional melancholia. The range varied from 12.3 to 47.8 seconds. There was a progressive increase in the mean circulation time dependent on the attack of the psychosis: first attack, 17.24 seconds; second attack, 22.06 seconds, and third attack, 23.65 seconds.

The mean circulation time for patients suffering from involutional melancholia was 19.94 seconds, suggestive of being significantly slower than the value for any other group except that with manic-depressive psychosis.

The mean circulation time for the 19 patients with toxic and organic psychoses was 15.15 seconds, a significantly faster rate of blood flow than that obtained for any other group.

The correlations between the circulation time and the pulse rate were significant for the entire group, the schizophrenic group and the psychopathic personality group, but not for the manic-depressive, involutional, psychoneurotic and toxic groups.

No correlations were obtained for the entire group or for any disease group between the circulation time and the age, height, weight, length of illness, permeability quotient, spinal fluid protein, blood sugar, blood nonprotein nitrogen, psychic tension, psychomotor activity or contact with environment.

BLOOD CHOLINE ESTERASE IN MYOTONIA CONGENITA AND MYASTHENIA GRAVIS

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Considerable interest has arisen concerning the role of cholinergic substances in myotonia congenita and myasthenia gravis. This has been stimulated by the recognition of the important part played by acetylcholine as a chemical transmitter of the parasympathetic impulses [1] and the demonstration of a specific blood esterase for its destruction.[2] It has been suggested that in myotonia there is an excess production of acetylcholine or an insufficient amount of esterase and that in myasthenia there is an insufficient amount of acetylcholine or an increase in esterase. Kennedy and Wolf [3] reviewed the evidence for and against these conceptions and concluded that neither adequately accounts for the facts; they suggested that the acidity of the muscle due to some metabolic disturbance may be changed sufficiently to affect the action of acetylcholine.

Determinations of values for acetylcholine esterase in the blood in cases of myasthenia gravis have given conflicting results. Stedman [4] and McGeorge,[5] using chemical methods, found the values to be low or within normal limits, while Hicks and MacKay,[6] using the biologic

From the Department of Pediatrics, University of Illinois College of Medicine.

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6. Hicks, C. S., and MacKay, M. E.: The Choline-Esterase Activity of Blood Serum from Two Cases of Myasthenia Gravis, Australian J. Exper. Biol. & M. Sc. **14**:275-289 (Dec.) 1936.

method, found them to be high. In a later study Hicks and MacKay,[7] again using the biologic method, observed low esterase values in cases of myotonia and a shift toward more normal values with clinical improvement after treatment with quinine.

In view of this speculation, the report of a study of the blood choline esterase in 5 patients with myotonia congenita, 2 patients with myasthenia gravis and 25 normal persons was considered timely. The continuous titration method as modified by Hall and Lucas[8] was used for the determinations.

Blood Esterase Values in Patients with Myotonia Congenita and Myasthenia Gravis Before and After Administration of Drugs

Values Used as Controls

Name	Age, Years	Sex	Esterase, Units: Average	Esterase, Units: Maximum	Esterase, Units: Minimum	Number of Determinations	Diagnosis
A. P.	37	M	3.34	3.75	2.91	7	Myotonia congenita
J. L.	24	M	4.67	4.97	4.24	7	Myotonia congenita
M. D.	27	M	3.06	3.44	2.35	6	Myotonia congenita
F. H.	5	M	3.78	3.88	3.68	2	Myotonia congenita
S. C.	12	F	4.09	....	....	1	Myotonia congenita
M. M.	20	F	2.75	....	....	1	Myasthenia gravis
A. G.	47	F	2.66	2.77	2.54	2	Myasthenia gravis
Normal adults			3.27	4.54	1.78	25	

Effect of Drugs Injected

Name	Esterase, Units: Before	Esterase, Units: After	Esterase, Units: Difference	Time Interval	Diagnosis	Clinical Effect
1 Mg. Prostigmine Subcutaneously						
M. M.	2.75	1.90	−0.85	1 hr.	Myasthenia gravis	Improvement
A. G.	2.77	2.36	−0.41	1 hr.	Myasthenia gravis	Improvement
M. D.	3.16	2.48	−0.68	½ hr.	Myotonia congenita	Exaggeration of symptoms
J. L.	4.97	4.14	−0.83	½ hr.	Myotonia congenita	Exaggeration of symptoms
6 Mg. Epinephrine Hydrochloride Intramuscularly						
M. D.	3.44	3.36	−0.08	½ hr.	Myotonia congenita	Exaggeration of symptoms
J. L.	4.56	4.81	+0.25	½ hr.	Myotonia congenita	Exaggeration of symptoms
1/100 Grain (0.6 Mg.) Atropine Sulfate Intramuscularly						
M. D.	2.35	2.38	+0.03	2 hr.	Myotonia congenita	No significant effect
J. L.	4.88	4.95	+0.07	2 hr.	Myotonia congenita	No significant effect
A. P.	3.75	3.76	+0.01	2 hr.	Myotonia congenita	No significant effect

The results of this study, as shown in the accompanying table, indicate that the values for blood acetylcholine esterase in both myotonia congenita and myasthenia gravis are within normal limits and do not support the idea that the defect in myotonia congenita and myasthenia gravis is primarily a modification of the blood esterase. Values for all the pathologic bloods fell essentially within the same range as those for

7. Hicks, C. S., and MacKay, M. E.: The Cholinesterase Content of Blood Sera from Normal and Myopathic Subjects, Australian J. Exper. Biol. & M. Sc. **16**:39-51 (March) 1938.

8. Hall, G. E., and Lucas, C. C.: Choline-Esterase Activity of Normal and Pathological Human Sera, J. Pharmacol. & Exper. Therap. **59**:34-41 (Jan.) 1937.

the normal bloods. This range was consistently higher than that reported by Hall and Lucas. Since our results agree in other particulars with those reported by Hall and Lucas, it is probable that a difference in the acetylcholine or some other constant condition is responsible for the shift in the range. The results are more consistent with the later view expressed by Kennedy and Wolf of a defect in acetylcholine efficiency. This may be secondarily influenced by the blood esterase, as shown by the action of prostigmine.

With the exception of prostigmine, none of the nine drugs used in the cases of myotonia had any significant effect on the blood acetylcholine esterase. The esterase was not significantly changed by epinephrine, which exaggerated the myotonia, or by quinine, which improved the myotonic condition.

We recognize that the esterase content of the blood does not necessarily reflect the concentration at the myoneural junction, but it is difficult to reconcile the clinical improvement in myasthenia gravis coincident with the decrease in blood esterase if there is no relation between the two concentrations. These results agree with those reported by Stedman and McGeorge and are in opposition to those reported by Hicks and MacKay. The latter authors, however, did not determine the esterase directly but assayed by biologic means the acetylcholine remaining after the esterase had been allowed to act a definite length of time, the reaction being inhibited with physostigmine. Whether this method gives a better estimate of esterase efficiency than the chemical method can be determined only by a comparison of the two methods with the same blood.

SUMMARY

1. Values for blood acetylcholine esterase in patients with myotonia congenita and myasthenia gravis fell within the same range as those of normal persons determined under the same experimental conditions.

2. Of the nine drugs investigated, prostigmine was the only substance which significantly affected the blood esterase.

3. The blood acetylcholine esterase in cases of myotonia congenita was not significantly changed when the clinical condition was exaggerated by epinephrine or when it was improved by quinine.

STUDIES IN DISEASES OF MUSCLE

VIII. METABOLISM OF CALCIUM, PHOSPHORUS AND MAGNESIUM IN PROGRESSIVE MUSCULAR DYSTROPHY, MYOTONIA ATROPHICA AND FAMILIAL PERIODIC PARALYSIS

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Although there is considerable evidence of the importance of calcium, phosphorus and magnesium in the chemical processes in voluntary muscle, no adequate studies of the metabolism of these substances in patients with muscular disease have heretofore been made. In the present investigation the metabolism of these minerals was studied in 4 patients. There were 2 patients with progressive muscular dystrophy, 1 with myotonia atrophica and 1 with familial periodic paralysis. In addition, the metabolism of calcium and phosphorus was investigated in another patient with myotonia atrophica, but the studies were not as extensive. Since the findings are in essential agreement with those on the other patient with this condition, they are not included in this report.

METHODS

The patients were kept in a special metabolism ward where careful collections of urine and feces could be made and where the diets were rigorously supervised. The mineral balance, for different levels of intake, was studied for periods of from five to seven days each, and there were from three to eight such periods for each patient. The amounts of calcium, phosphorus and magnesium in the diet varied in the different periods, but were kept constant from day to day in each period. Each experimental period was preceded by a preliminary period of about six days, during which the intake of minerals was the same as that of the following experimental period. The mineral content of the diets as calculated from the values given by Sherman [1] was checked by chemical analysis of duplicate diets. During one period of observation 1 patient with progressive muscular dystrophy was given a preparation of cottonseed flour. The cottonseed flour was included in the diet because of its high content of phosphorus and magnesium. Since this preparation is free from creatine and creatinine, its use permitted the simultaneous study of the metabolism of creatine and creatinine. Most of the other foodstuffs, such as meat, which contain large amounts of phosphorus and magnesium, also contain creatine and therefore are unsatisfactory when diets free from creatine and creatinine are required.

From the New York Hospital and the Department of Medicine, Cornell University Medical College, and the Russell Sage Institute of Pathology.

1. Sherman, H. C.: Chemistry of Food and Nutrition, ed. 4, New York, The Macmillan Company, 1932.

The urine was collected carefully in twenty-four hour specimens and analyzed daily for the content of nitrogen, calcium, phosphorus and magnesium. The feces of the several periods were marked off by carmine ingested by the subjects. The specimens of feces belonging to each period were put together, dried on the steam bath and ashed for the subsequent determinations of the minerals. The calcium in the urine and feces was determined by the methods of Shohl and Pedley [2] and McCrudden,[3] respectively. The phosphorus was determined by the technic of Fiske and Subbarow,[4] and the magnesium was estimated by the method of McCrudden [3] by using the filtrate obtained after the precipitation of the calcium.

Average Daily Balances of Calcium, Phosphorus and Magnesium

		Intake, Mg.			Output, Mg.						Balances, Mg.		
					Urinary			Fecal					
Data on Patient	Period No.	Calcium	Phosphorus	Magnesium	Calcium	Phosphorus	Magnesium	Calcium	Phosphorus	Magnesium	Calcium	Phosphorus	Magnesium
Case 1, progressive muscular dystrophy, S., female, 29 yr., 54 Kg.	I	1,002	1,502	223	194	1,143	124	678	375	98	130	— 16	1
	II	102	619	157	77	526	83	175	218	101	—150	—125	—27
	III	1,004	1,462	209	198	1,103	102	770	394	89	36	— 35	18
	IV	2,003	1,932	306	266	1,480	138	1,133	447	139	604	— 25	29
	V	1,002	1,501	223	232	1,196	102	947	438	109	—177	—130	12
	VI	4,001	3,413	350	397	2,535	89	2,520	992	184	1,084	86	77
	VII	4,001	3,413	350	413	2,326	115	2,300	888	187	1,287	199	48
	VIII	100	325	115	97	266	66	125	182	108	—122	—123	—53
Case 2, progressive muscular dystrophy, P., male, 16 yr., 40.7 Kg.	I	1,001	1,157	229	28	734	100	620	395	119	353	128	10
	II	1,001	1,157	229	32	678	96	676	412	121	293	67	12
	III	102	519	157	27	385	59	62	128	73	13	6	25
	IV	102	519	157	14	393	59	79	164	96	9	— 38	2
	V	2,003	1,932	306	58	961	122	1,382	790	169	563	181	15
	VI	2,003	1,932	306	41	943	120	1,530	1,006	156	432	— 17	30
	VII	1,007	1,452	166	42	910	77	666	494	92	299	48	— 3
	VIII†	508	1,623	515	38	753	96	330	680	386	140	190	33
Case 3, myotonia atrophica, A., male, 48 yr., 53 Kg.	I	118	672	224	92	517	61	115	271	161	— 89	—116	2
	II	1,008	1,498	217	219	1,013	57	889	474	108	—100	11	52
	III	1,974	1,992	388	194	1,092	58	1,543	762	267	237	138	63
Case 4, familial periodic paralysis, N., male, 15 yr., 55 Kg.	I	1,008	1,452	166	196	1,291	72	669	523	65	143	—362	29
	II	2,003	1,932	306	244	1,358	128	1,180	728	78	579	—144	100
	III	102	627	162	173	635	78	183	270	83	—254	—378	1

* The number of days in each experimental period in each case was as follows: case 1, 6; case 2, 5; case 3, 7, and case 4, 6, except in period I, in which there were 12 days.

† The daily diet included 50 Gm. of cottonseed flour (Cofio), containing 111 mg. of calcium, 615 mg. of phosphorus and 311 mg. of magnesium. The flour was furnished by the Traders' Oil Mill Co., Fort Worth, Texas.

OBSERVATIONS

The data are shown in detail in the accompanying table and will be summarized briefly.

2. Shohl, A. T., and Pedley, F. G.: A Rapid and Accurate Method for Calcium in the Urine, J. Biol. Chem. **50**:537, 1922.

3. McCrudden, F. H.: The Quantitative Separation of Calcium and Magnesium in the Presence of Phosphates and Small Amounts of Iron Devised Especially for the Analysis of Foods, Urine and Feces, J. Biol. Chem. **7**:83, 201, 1909-1910.

4. Fiske, C. H., and Subbarow, Y.: The Colorimetric Determination of Phosphorus, J. Biol. Chem. **66**:375, 1925.

Calcium.—In all 4 subjects the balance of calcium was normal, except in patient P. (case 2), who retained appreciable amounts of calcium with an intake of 1,001 mg. For several years the diet of this patient, a boy aged 16, with progressive muscular dystrophy, had been definitely low in calcium.

Calcium Balance

	Intake		
	High	Normal	Low
Case 1.....	++	0	—
Case 2.....	++	++	0
Case 3.....	+	—	—
Case 4.....	++	+	—

(Balance 0 indicates that output and intake were equal.)

Phosphorus.—The balance of phosphorus was normal in all the subjects, with the outstanding exception of patient N (case 4), with familial periodic paralysis. Even with a relatively high phosphorus intake of 1,932 mg. daily there was a negative balance, with a daily loss of 144 mg. When the intake was 1,452 mg. the negative balance amounted to 362 mg. daily, and with a low intake of 627 mg. the daily loss was 378 mg. In brief, the patient's output of phosphorus exceeded the intake for the entire period of forty-two days during which observations were made.

Phosphorus Balance

	Intake		
	High	Normal	Low
Case 1.....	+	0	—
Case 2.....	+	0	0
Case 3.....	+	0	—
Case 4.....	—	— —	— —

(Balance 0 indicates that output and intake were equal.)

The concentrations of calcium and phosphorus in the blood serum of patient N (case 4) were essentially normal, namely, 11.4 and 5.2 mg., respectively, per hundred cubic centimeters.

Magnesium.—The balance of magnesium was normal in the 4 patients with intakes varying from 115 to 515 mg. daily. All 4 patients were in balance when the daily intake was about 200 mg.

COMMENT

Many investigations have been made on the metabolism of creatine in muscular diseases, but relatively little attention has been given to the metabolism of the minerals in these conditions, although the importance of the minerals in the physiologic processes of muscle is now well recognized. Nevin [5] determined the amounts of phosphorus-holding compounds in the muscles of patients with progressive muscular dystrophy and myotonia atrophica. He concluded that the alterations which occurred in the amounts of these substances were secondary to the degeneration of the muscle and that they were not significantly related

5. Nevin, S.: A Study of the Muscle Chemistry in Myasthenia Gravis, Pseudo-Hypertrophic Muscular Dystrophy and Myotonia, Brain **57**:239, 1934.

to the nature of the disease process itself. Pemberton [6] found a normal calcium balance in 1 patient with myotonia atrophica studied for a period of five days. Rosenbloom and Cohoe,[7] in their studies on a patient with "myotonia" without muscular wasting (myotonia congenita), observed a loss of 3.15 Gm. of calcium over a period of ten days when the total intake for the period was 21.87 Gm. The magnesium balance was normal. The observations of Ribadeau-Dumas, Bourguignon and Lévy [8] were not concerned directly with the metabolism of calcium, but they are suggestive in that the administration of viosterol to a child with myotonia congenita was followed by improvement in the functional defect of the muscles. Keschner and Davison [9] and Morgulis and Young [10] found the concentration of calcium in the serums of patients with myotonia atrophica to be normal. Janney, Goodhart and Isaacson [11] observed retention of calcium and magnesium in a case of progressive muscular dystrophy, but since the period of study was only three days, the data are not convincing.

In the present studies no significant abnormality in the metabolism of calcium, phosphorus or magnesium could be demonstrated in the patients with progressive muscular dystrophy or myotonia atrophica. The positive balance of calcium in 1 patient with progressive muscular dystrophy is considered to have been the result of his previous diet. For several years the calcium intake of the patient had been abnormally low.

Probably the most significant observations on the mineral metabolism in muscular disease are those of Aitken, Allott, Castleden and Walker [12] in a patient with familial periodic paralysis. These investigators observed the level of potassium in the blood serum to be abnormally low during the attacks of muscular paralysis. Administration of potassium chloride in sufficient amounts abolished the paralysis. On the other hand, ingestion of dextrose lowered the level of the serum potassium more than in

6. Pemberton, R.: A Metabolic Study of Myotonia Atrophica, Am. J. M. Sc. **141**:253, 1911.

7. Rosenbloom, J., and Cohoe, B. A.: Clinical and Metabolism Studies in a Case of Myotonia Congenita—Thomsen's Disease, Arch. Int. Med. **14**:263 (Aug.) 1914.

8. Ribadeau-Dumas, L.; Bourguignon, and Lévy, M.: Atonie congénitale, hypocalcémie, amélioration remarquable par les grosses doses de stérol irradié, Bull. Soc. de pédiat. de Paris **29**:110, 1931.

9. Keschner, M., and Davison, C.: Dystrophica Myotonica: A Clinicopathologic Study, Arch. Neurol. & Psychiat. **30**:1259 (Dec.) 1933.

10. Morgulis, S., and Young, A.: Metabolism in Myotonia Atrophica: Report of a Case, Arch. Int. Med. **48**:569 (Oct.) 1931.

11. Janney, N. W.; Goodhart, S. P., and Isaacson, V. I.: The Endocrine Origin of Muscular Dystrophy, Arch. Int. Med. **21**:188 (Feb.) 1918.

12. Aitken, R. S.; Allott, E. N.; Castleden, L. I. M., and Walker, M.: Observations on a Case of Familial Periodic Paralysis, Clin. Sc. **3**:47, 1937.

normal subjects and was followed by an attack of paralysis. The authors concluded that lowering of the potassium concentration either blocks neuromuscular transmission or inhibits the contractile response in the muscles affected. The finding of a low concentration of serum potassium during an attack of paralysis has been confirmed by Ferrebee, Atchley and Loeb;[13] Gammon,[14] and Pudenz, McIntosh and McEachern.[15] Ferrebee, Atchley and Loeb observed a fall in the excretion of urinary potassium during an attack and a compensating increase in the output of potassium following an attack. It is of interest that while the patient studied by Aitken, Allott, Castleden and Walker had an attack of muscular paralysis whenever the concentration of serum potassium fell below 12 mg. per hundred cubic centimeters, the 2 patients observed by Harrop and Benedict[16] and the 1 studied by Kerr[17] had no such disturbance even when the serum potassium fell as low as 8.5 or 7.2 mg. per hundred cubic centimeters. These 3 patients were diabetic subjects who were given insulin.

When considered together, the observations suggest that in familial periodic paralysis the lowered serum potassium is only one factor in the causation of the attacks. It appears probable that at least one other defect in the physiologic mechanism of the neuromuscular unit must be present in order that muscular paralysis will occur when the serum potassium is lowered to the level indicated by the studies of Aitken, Allott, Castleden and Walker.

The present studies show that during the entire period of investigation the patient with familial periodic paralysis showed a definite abnormality in the balance of phosphorus. In contrast to the 2 patients with progressive muscular dystrophy and the 2 with myotonia atrophica, in whom the balance of phosphorus was normal, this patient showed a constantly negative phosphorus balance. This defect in the phosphorus metabolism was not accompanied by any disturbance in the metabolism of calcium or magnesium. The fact that there was no concomitant loss of calcium suggests that the phosphorus came from a site other than the

13. Ferrebee, J. W.; Atchley, D. W., and Loeb, R. F.: A Study of the Electrolyte Physiology in a Case of Familial Periodic Paralysis, J. Clin. Investigation **17**:504, 1938.

14. Gammon, G. D.: Relation of Potassium to Family Periodic Paralysis, Proc. Soc. Exper. Biol. & Med. **38**:922, 1938.

15. Pudenz, R. H.; McIntosh, F. F., and McEachern, D.: The Role of Potassium in the Mechanism of Family Periodic Paralysis, J. Clin. Investigation **17**:530, 1938.

16. Harrop, J. A., and Benedict, E. M.: The Participation of Inorganic Substances in Carbohydrate Metabolism, J. Biol. Chem. **59**:683, 1924.

17. Kerr, S. E.: The Effect of Insulin and of Pancreatectomy on the Distribution of Phosphorus and Potassium in the Blood, J. Biol. Chem. **78**:35, 1928.

bones. Probably this site was the muscles, which normally contain large amounts of this mineral.

In support of this view is the finding of Brand and Harris [18] of a low concentration of phosphorus in the muscle of a patient with familial periodic paralysis. Whereas the muscle of a normal subject contained 143 mg. of total acid-soluble phosphorus in each 100 Gm. of tissue, the muscle of their patient contained only 76 mg. The concentration of creatine in the muscle was reduced also. Clinical and histologic studies showed no evidence of muscular wasting (Zabriskie and Frantz [19]).

The metabolism of creatine and creatinine was studied in patient N. (case 4), but the detailed data are not given in this report. The output of creatinine was normal; there was no significant creatinuria, and the ability to retain ingested creatine (creatine tolerance) was only slightly less than that in most normal subjects.

The observations which were made for a period of forty-two days followed a short series of attacks of paralysis. No paralysis occurred while the patient was in the hospital or for the four months following his discharge. In other words, the loss of phosphorus was found to occur shortly after attacks during a period in which the patient was free from paralysis. Whether the negative balance was present at other times is not known. However, it seems unlikely that the patient would show a persistent loss of phosphorus without the development of structural defects, and all evidence of structural change was lacking. It appears probable that phosphorus is lost in large amounts at certain times in the course of familial periodic paralysis and that storage of phosphorus occurs during other periods. It was impossible to study the phosphorus balance of this patient, either during a period of attack or just before an attack. Hence, the storage of phosphorus during these periods can only be postulated. However, the evidence available at present shows that during certain periods in the course of familial periodic paralysis in this patient there was a definite negative phosphorus balance.

SUMMARY

The balances of calcium, phosphorus and magnesium were studied in 2 patients with progressive muscular dystrophy, 1 patient with myotonia atrophica and 1 patient with familial periodic paralysis.

The balances of these minerals were normal in the patients with progressive muscular dystrophy and myotonia atrophica, except that in a

18. Brand, E., and Harris, M. M.: Phosphorus Metabolism in Muscular Disease, J. Biol. Chem. **97**:lxii, 1932.

19. Zabriskie, E. G., and Frantz, A. M.: Family Periodic Paralysis, Bull. Neurol. Inst. New York **2**:57, 1932.

patient with progressive muscular dystrophy whose previous diet had been deficient in calcium there was a positive calcium balance even when the intake was low.

In the patient with familial periodic paralysis a definite defect in the metabolism of phosphorus was found. Whereas the balances of calcium and magnesium were normal, the balance of phosphorus was persistently negative over a period of forty-two days. Significant amounts of phosphorus were lost even when the diet contained large amounts of this mineral. It appears likely that the source of the phosphorus was the muscles rather than the bones. The observations were made after the occurrence of attacks of paralysis. Whether a similar loss of phosphorus precedes an attack of paralysis or whether phosphorus is retained at that time is not known.

CASE HISTORIES

CASE 1.—*Progressive muscular dystrophy.*

S., a woman aged 29, had complained of weakness and wasting of the muscles of the arms and legs since the age of 12. The disability increased slowly but steadily. For the past four years she had been bedridden and unable to lift the arms above the waist line. A sister who was similarly affected died at the age of 33.

Examination showed extreme muscular disability. The patient could sit up only with support, and the arms could not be lifted from the bed. There was considerable wasting of the muscles of the shoulders and upper parts of the arms. The calves were of normal size, but there was almost complete loss of muscular power. The patient weighed 54 Kg.

CASE 2.—*Progressive muscular dystrophy.*

P., a boy aged 16, began to complain of muscular weakness at the age of 7 years. The weakness was first noted in the muscles of the legs, but soon progressed rapidly and involved the muscles of the arms and trunk. For the five years preceding his admission the patient had been confined to bed. The past personal history was irrelevant except that for several years the diet had been extremely low in calcium.

Examination revealed extreme wasting of the muscles of all the extremities and of the trunk. There were considerable scoliosis and lordosis. Both feet showed advanced foot drop. Because of the generalized muscular weakness the patient was able to perform only the most limited voluntary movements. He weighed 40.7 Kg.

CASE 3.—*Myotonia atrophica.*

A., an elevator operator aged 48, complained of increasing weakness and difficulty in walking for three years. For the same period he had difficulty in relaxing the muscles of his hands after an initial forceful contraction. After a few trials the difficulty would disappear only to return again after a period of rest. The patient walked with a cane.

Examination revealed bilateral wasting and weakness of the sternocleidomastoid, pectoral and deltoid muscles and weakness of the tibialis muscles. The profile was of the "hatchet" type, and there was weakness of the orbicular muscles of the eyes and mouth and of the masseter and temporal muscles. When the

muscles of the tongue and forearms were struck, a slow wave of contraction appeared at the site of the blow. The knee jerks were weak, and the ankle jerks were absent. The patient weighed 53 Kg.

CASE 4.—*Family periodic paralysis.*

N., a boy aged 15, complained of periodic attacks of paralysis involving most of the voluntary muscles. The first of these attacks occurred two months prior to his admission to the hospital. Up to the time of his admission the patient had had five attacks, all of similar character. Without any premonitory symptoms, the patient suddenly became unable to move the muscles of the arms, legs nad neck. There was no difficulty with respiration or with control of the sphincters. Consciousness was unimpaired, and sensibility for pinprick was normal. Four of the attacks followed the ingestion of large meals rich in carbohydrates. The duration of the attacks varied from less than an hour to twenty-four hours. The family history was of interest in that the patient's father had had several attacks of muscular paralysis since the age of 15 years.

Examination of the patient during an interval when he was free from attacks revealed no evidence of any abnormality. He weighed 55 Kg.

EFFECT OF BENZEDRINE SULFATE AND PHENOBARBITAL ON BEHAVIOR PROBLEM CHILDREN WITH ABNORMAL ELECTROENCEPHALOGRAMS

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In a previous report from the Emma Pendleton Bradley Home [1] it has been shown that medication with benzedrine sulfate had a beneficial effect on certain children with severe behavior problems. It has also been reported [2] that over half a group of 71 behavior problem children from this hospital showed distinctly abnormal electroencephalograms. The question arises as to a possible relationship between the beneficial effects of benzedrine sulfate and the functional abnormalities of the brain as revealed by the electroencephalogram. Since the type of brain potentials observed and the personality deviations in these patients often suggested an epileptiform disorder of the brain, the effect of phenobarbital therapy alone and in combination with benzedrine was also studied.

CASE MATERIAL

Twelve behavior problem children, 2 girls and 10 boys, between 7 and 10 years of age were selected for intensive study. These children were all admitted to the hospital because of erratic and asocial behavior which was not controlled. They all presented the same type of problem. They were described as hyperactive, impulsive and destructive, with marked variations in personality unrelated to adequate changes in the environment. There were no positive neurologic findings at the time of examination. One patient had a family history of epilepsy; only 1 had had convulsions. No clinical convulsions were observed in any of these patients during their stay in the hospital, which varied from four to thirty-six months, with an average of eleven months. Intelligence quotients ranged from 70 to 126, with an average of 91. All of this group were classified as "epileptoid" on the basis of both the clinical and the electroencephalographic findings as described in a previous paper,[2] which included descriptive case reports.

The studies were carried out at the Emma Pendleton Bradley Home.
This investigation was supported by a grant from the Rockefeller Foundation.

1. Bradley, C.: Behavior of Children Receiving Benzedrine, Am. J. Psychiat. **94**:577-585, 1937.

2. Jasper, H. H.; Solomon, P., and Bradley, C.: Electroencephalographic Analyses of Behavior Problem Children, Am. J. Psychiat. **95**:641-658, 1938.

METHOD

Electroencephalographic examinations were made according to the procedures previously described.[3] Records from both bipolar and monopolar leads to the right and left frontal, central and occipital regions were taken under standard conditions. Simultaneous tracings from four regions of the head were recorded by means of a crystal ink-writing oscillograph as well as photographically with the Westinghouse mirror oscillographs. A trained observer sat in the shielded quiet room with the patient, signaled all movements directly on the record and noted the condition of the patient throughout each examination.

The clinical status of each patient was determined from extensive nurses' notes taken daily, as well as reports from the schoolteachers, playground instructors and physicians. Special emphasis was placed on variations in personality and changes in reactions to standard environmental situations. Only the most outstanding differences agreed on by all observers were considered as indicative of a genuine change due to a given form of medication.

Preliminary clinical and electroencephalographic studies were made on each child before any form of medication. These examinations were repeated after each patient had received 20 mg. of benzedrine sulfate (in divided doses) per day for at least six days. A third examination was made three days after the addition of phenobarbital, 1½ grains (0.097 Gm.) per day. Then a fourth examination was made after administration of phenobarbital alone for two days following the withdrawal of benzedrine.

A minimum of four complete examinations was made on each patient under the conditions described. Records were repeated on different days without any change in medication in 10 cases to obtain an indication of the reliability of a given record. A total of 54 records were analyzed for the present report. Per cent time measurements of the amount of regular alpha wave activity, at frequencies between 7.5 and 15 per second, were made for bipolar and monopolar leads to the frontal, central and occipital regions of the head. Similar measurements were made of the amount of slow wave activity at frequencies below 7 per second. The variation in these measurements from day to day in the same patient was found to be not more than 10 per cent, which is in accord with reliabilities found by other authors.[4] Frequencies, amplitudes, regularity, differences between the two sides and major potential patterns were noted in the analysis of each record.

RESULTS

Electroencephalographic Findings with No Medication.—Two distinct types of brain potential patterns were found to an abnormal degree in the 12 behavior problem children selected for this study.

1. The 6 Cycle Rhythm: Seven patients showed a distinct regular rhythm of 5 to 7 per second, these waves occurring chiefly in the central and frontal regions of the head (fig. 1 *A*), but sometimes spreading into the occipital region. (This rhythm was called the "subalpha rhythm" in the previous report, but since it is so completely independent of the alpha rhythm it was thought necessary

3. Jasper, H. H., and Andrews, H. L.: Electro-Encephalography: III. Normal Differentiation of Occipital and Precentral Regions in Man, Arch. Neurol. & Psychiat. **39**:96-115 (Jan.) 1938.

4. Davis, H., and Davis, P. A.: Action Potentials of the Brain in Normal Persons and in Normal States of Cerebral Activity, Arch. Neurol. & Psychiat. **36**:1214-1224 (Dec.) 1936.

to abandon this terminology.) It may appear in short bursts of 3 or 4 waves at intervals of several seconds or in trains of 20 to 30 waves with a regularity and form found in a good alpha rhythm. The amplitude is also comparable with that of the alpha rhythm. It seems to have an independent origin, since it often appears simultaneously with superimposed alpha or beta waves. It is unaffected by visual stimulation, which blocks the alpha rhythm, and it persists superimposed on some of the slower potentials of sleep. In some cases 3 per second "petit mal waves" appeared without affecting the continued presence of the 6 cycle rhythm. The 6 cycle waves often appeared in sudden large bursts suggestive of an epileptiform disturbance. They were probably related to the waves reported by Gibbs, Gibbs and Lennox [5] as associated with attacks of "psychomotor epilepsy."

2. Slow Waves and Irregular Activity: Eight patients showed potentials slower than the 6 cycle rhythm, usually occurring at random intervals in a disorganized manner with occasionally a few waves which were of sufficient regularity to be assigned a frequency of from 2 to 4 per second (fig. 1 *B*). These slow waves did not appear with any constant form or amplitude, but seemed to be just random potential fluctuations which in the more severe conditions occupied almost the entire record from any region of the head. In patients presenting some normal alpha rhythm the slow waves either periodically took the place of the alpha rhythm or appeared with the alpha rhythm superimposed on them. In 3 cases of this type the irregularity seemed to include also the frequency of the alpha rhythm, causing variations of from 8 to 12 per second in consecutive spindles, and even within a single spindle of 5 to 10 waves. Although occasionally 1 or 2 waves with a "spike" and slow wave form were seen in 2 of these cases, we have not observed in any instance a typical series of waves of the type described by Gibbs and his associates [6] as characteristic of petit mal epilepsy. The record from a patient showing both the slow waves in the occiput and the 6 cycle rhythm in the frontal and central regions is shown in figure 1 *C*.

Effects of Medication.—Benzedrine did not appear to have a definite effect on any aspect of the electroencephalogram of these patients. Measurements of the per cent time alpha wave activity with both monopolar and bipolar leads to the three regions of the head did not reveal any significant differences during benzedrine medication, as shown in the accompanying table of averages. Neither was the 6 cycle rhythm or the slow wave activity affected to any appreciable extent by benzedrine (fig. 2). In 8 of the 12 patients the per cent time measurements of slow waves before and those during benzedrine medication did not differ more than 10 per cent. In only 1 case was a decrease of over 10 per cent in the slow wave activity observed with benzedrine, while an increase of over 10 per cent in slow wave activity was observed in 3 cases.

Definite changes in the electroencephalogram were produced by phenobarbital, although the nature of the changes depended on the type of activity present before the medication. The 6 cycle rhythm was increased in amplitude and amount in cases in which this rhythm was present with no medication. The slower waves of the random type and with frequencies of 2 to 4 per second

5. Gibbs, F. A.; Gibbs, E. L., and Lennox, W. G.: Cerebral Dysrhythmias of Epilepsy: Measures for Their Control, Arch. Neurol. & Psychiat. **39**:298-314 (Feb.) 1938.

6. Gibbs, F. A.; Davis, H., and Lennox, W. G.: Electro-Encephalogram in Epilepsy and in Conditions of Impaired Consciousness, Arch. Neurol. & Psychiat. **34**:1133-1148 (Dec.) 1935.

were decreased in amplitude and amount, with more of the type of activity approaching the normal, during phenobarbital medication in the cases in which a large amount of this type of activity was present without medication. These findings were confirmed in the records taken with a combination of pheno-

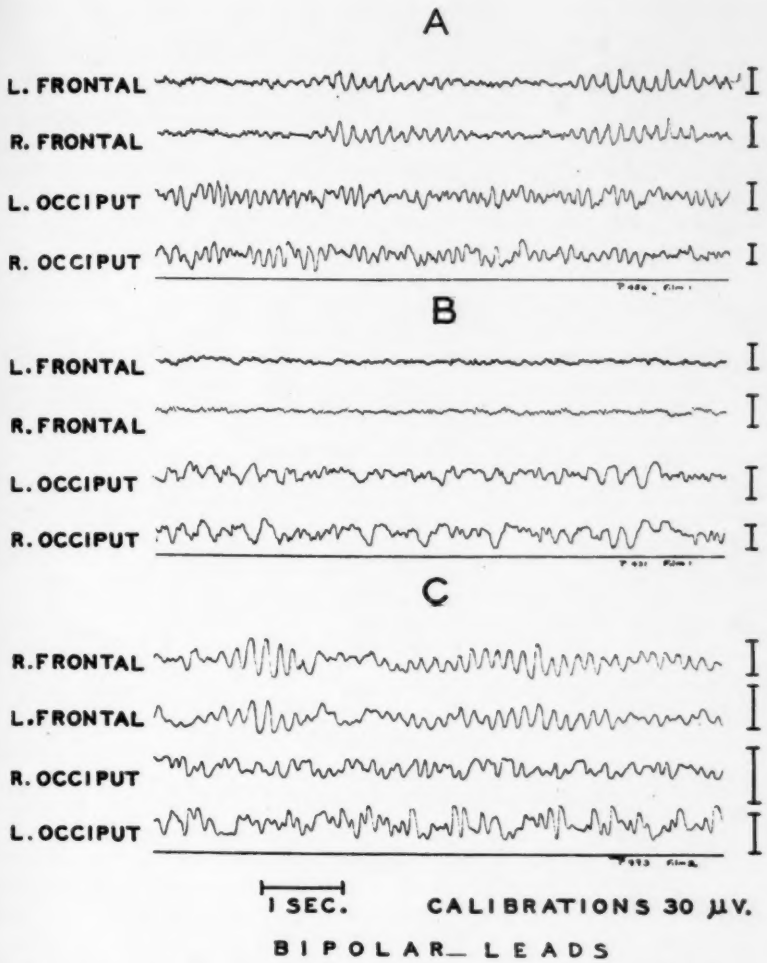

Fig. 1.—Sample electroencephalograms in (*A*) a case in which there was a 6 cycle rhythm in the frontal regions with alpha waves in the occipital regions; (*B*) a case in which random slow activity was shown, and (*C*) a case in which there was a combination of random slow activity and the 6 cycle rhythm.

barbital and benzedrine, since the benzedrine did not appear to alter the records. Owing to the varied effects of this drug in individual cases, the averages shown in the table tend to mask the specific results.

The most striking effect of phenobarbital in 10 of the 12 cases was an increase in the amplitude and number of beta (24 to 32 per second) waves. With the

bipolar leads this was most marked from the central and frontal regions of the head, but with the monopolar leads it was clear from all regions. Amplitudes of beta waves reached as high as 100 microvolts and were present throughout a long record during phenobarbital medication in patients who showed only a trace of low amplitude beta activity previous to administration of the drug. The beta waves were present also when benzedrine was combined with phenobarbital, but were absent with benzedrine alone. The most extreme example of this change is shown in figure 2.

The percentage of the records composed of regular alpha wave activity was reduced in 8 of the 12 patients with phenobarbital medication. This tendency is also shown in the table of averages, especially in the occipital monopolar records. Since the amount of alpha wave activity was increased somewhat with the addition of benzedrine to the phenobarbital and since we found it difficult to keep the patients wide awake with phenobarbital alone, the decrease in alpha wave activity may have been due to drowsiness.[7]

Effects of Benzedrine Sulfate and Phenobarbital on the Electroencephalograms of Behavior Problem Children

Lead	No Medication	Benzedrine Sulfate	Phenobarbital	Benzedrine Sulfate and Phenobarbital
	Mean Per Cent Alpha Waves			
Frontal bipolar	23	28	23	22
Central bipolar	40	42	37	32
Occipital bipolar	58	61	59	61
Frontal monopolar	39	37	33	34
Central monopolar	40	41	44	41
Occipital monopolar	69	57	53	61
	Mean Per Cent Slow Waves			
Frontal bipolar	19	25	19	17
Central bipolar	22	25	18	18
Occipital bipolar	23	30	22	24
Frontal monopolar	36	26	25	24
Central monopolar	35	33	28	28
Occipital monopolar	28	25	28	27

CORRELATIONS WITH CHANGES IN BEHAVIOR

Clinical improvement with benzedrine medication was noted in 7 of the 12 cases. The children became less active and impulsive and more cooperative and prompt in their hospital routine. The teachers noted improvement in interest and efficiency, with a lengthened span of attention. Attendants completely unaware of the medication remarked spontaneously that a change in behavior had occurred.

The electroencephalogram in all cases in which there was improvement with benzedrine was characterized by predominance of the 6 cycle pattern. One

7. Jasper, H. H.: Cortical Excitatory State and Synchronism in the Control of Bioelectric Autonomous Rhythms, in Cold Spring Harbor Symposia on Quantitative Biology, Cold Spring Harbor, L. I., New York, The Biological Laboratory, 1936, vol. 4, pp. 320-338. Loomis, A. L.; Harvey, E. N., and Hobart, G.: Potential Rhythms of the Cerebral Cortex During Sleep, Science **81**:597-598, 1935; Further Observations on Potential Rhythms of the Cerebral Cortex During Sleep, ibid. **82**:198-200, 1935.

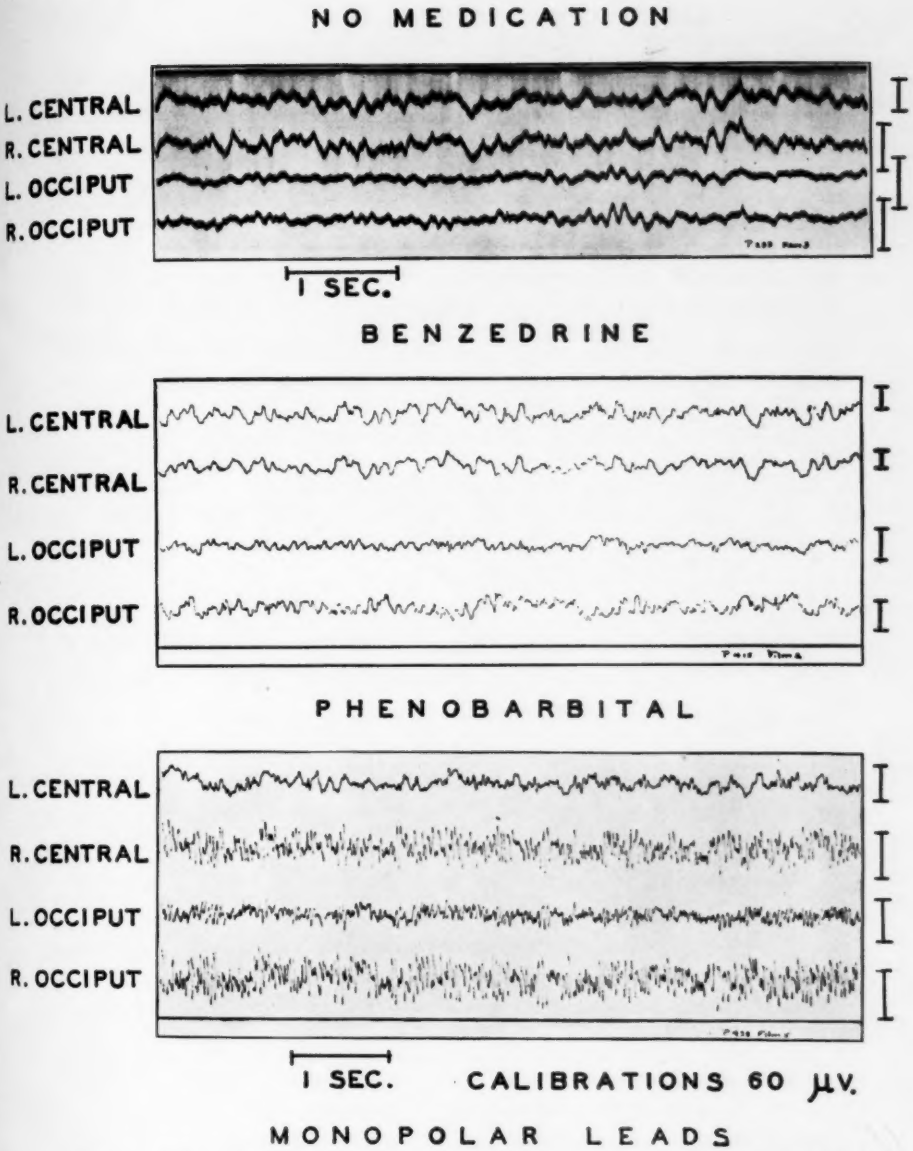

Fig. 2.—Effect of benzedrine sulfate and phenobarbital on the electroencephalogram. The first record was taken with optical oscillographs, the other two with ink-writing recorders.

child whose behavior was not changed by benzedrine showed a considerable amount of 6 cycle activity in the electroencephalogram, but also much of the slower and random wave activity together with irregularities of the alpha rhythm. The remaining 4 patients who did not improve with benzedrine showed the slower random waves without the 6 cycle rhythm.

This correlation between benzedrine therapy and a 6 cycle rhythm in the electroencephalogram is confirmed in a group of 15 behavior problem children now being studied at this hospital. Fourteen of the 15 children improved with benzedrine and showed a prominent 6 cycle rhythm in the electroencephalogram. The only child who did not improve showed together with the 6 cycle activity other abnormalities in the electroencephalogram similar to those in the case previously mentioned.

In contrast to the beneficial effects of benzedrine in certain cases, phenobarbital caused a definite exacerbation of symptoms in 9 of the 12 cases; in the remaining 3 cases no apparent clinical change was shown. The usual reaction was that of extreme irritability, marked by temper tantrums and impulsive destructive behavior with no apparent external cause, or, on the other hand, grimacing and silly giggling. Some of this behavior was probably related to the tendency to drowsiness already mentioned.

The increase in beta wave activity in the electroencephalograms of 10 patients given phenobarbital does not appear to be related to the exacerbation of clinical symptoms, since 2 children without an increase in beta wave activity were worse clinically. Conversely, the 3 children who were not made clinically worse with phenobarbital all had an increase in beta wave activity.

COMMENT

The present study has served to clarify the disorder in a specific group of behavior problem children who have been called epileptoid because of personality characteristics and electroencephalograms similar to those of epileptic patients. In about one-half the cases in this group there appears to be a more specific disorder, identified by a favorable response to benzedrine and the presence of a prominent 6 cycle rhythm in the electroencephalogram. This group of cases probably represents the same disorder in children as that described by Gibbs and his associates [8] as "psychomotor epilepsy" in adults. These authors also found in such cases that phenobarbital tends to increase rather than to decrease the number and severity of the attacks.

The number of patients in the present study is too small to assure a perfect correlation between the 6 cycle rhythm in the electroencephalogram and susceptibility to benzedrine therapy. One might well expect to find in patients without this specific disorder of the brain, marked changes due to the administration of a drug which produces such gen-

8. Gibbs, F. A.; Gibbs, E. L., and Lennox, W. G.: The Effect on the Electro-Encephalogram of Certain Drugs Which Influence Nervous Activity, Arch. Int. Med. **60**:154-166 (July) 1937; Epilepsy: A Paroxysmal Cerebral Dysrhythmia, Brain **60**:377-388, 1937.

eralized changes in the condition of the autonomic nervous system as does benzedrine.[9]

The fact that marked changes in behavior may occur in patients receiving benzedrine or phenobarbital therapy without corresponding changes in the electroencephalogram raises the question of the physiologic action of these drugs. There is sufficient evidence that abnormalities in the electroencephalogram indicate defects in brain function, even though the specific nature of the pathologic change is not determined by this method. The changes in personality with benzedrine are probably due to an alteration in the patient's emotional reactions to the type of brain disorder revealed in the electroencephalogram without any fundamental change in the disorder itself. Since the brain potentials recorded through the skull are chiefly of cortical origin, the benzedrine may act on subcortical centers which are not closely related to the type of cortical function shown in the electroencephalogram. This may be suspected from the fact that benzedrine is known to affect particularly the autonomic nervous system. As practically nothing is known at present regarding the cause or origin of the 6 cycle rhythm, which seems to be the important abnormality in the electroencephalogram of these patients, we think that further speculation is at present not justified.

SUMMARY

The effect of benzedrine sulfate and phenobarbital has been studied on 12 behavior problem children with abnormal electroencephalograms. A fairly homogeneous clinical and electroencephalographic entity has been described and called epileptoid. About one half of these patients were distinguished by marked improvement in behavior with benzedrine therapy and by the presence of a prominent 6 cycle rhythm in the electroencephalogram. Phenobarbital is definitely contraindicated in the treatment of these children. Changes in the electroencephalogram were not observed to correlate with the clinical changes produced by these drugs.

9. Myerson, A.: Effect of Benzedrine Sulfate on Mood and Fatigue in Normal and in Neurotic Persons, Arch. Neurol. & Psychiat. **36**:816-822 (Oct.) 1936. Myerson, A.; Loman, J., and Dameshek, W.: Physiologic Effects of Benzedrine and Its Relationship to Other Drugs Affecting the Autonomic Nervous System, Am. J. M. Sc. **192**:560-574, 1936.

ETIOLOGIC FACTORS IN EXPERIMENTALLY PRODUCED PONTILE HEMORRHAGES

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The association of pontile hemorrhages with space-consuming intracranial lesions has been frequently noted. Attwater,[1] in 1911, studied 67 cases of traumatic and apoplectic hemorrhages and observed that in 30 per cent they were accompanied by pontile lesions. In 1917, Greenacre [2] found multiple nontraumatic cerebral hemorrhages in the region of the basal ganglia and in the pons in 8.5 per cent of 128 cases. Wilson and Winkelman,[3] in 1926, studied 129 cases of various space-consuming intracranial lesions and observed accompanying pontile lesions in 9.9 per cent. Rosenhagen [4] observed tegmental and pontile hemorrhages in 10 of 19 cases of tumors of the brain which he studied. Moore and Stern [5] demonstrated hemorrhage into the pons in 9.3 per cent of cases of varying lesions associated with increased intracranial pressure.

An attempt to explain the pathogenesis of this type of lesion has resulted in many hypotheses. Attwater [1] suggested that the increased intracranial pressure and a degenerated condition of the pontile arteries were responsible for these lesions. Greenacre [2] offered the explanation that the increased arterial pressure, together with the unusual strain afforded by backflow from the carotid artery when the middle cerebral artery on that side had been occluded, was sufficient to cause rupture of such small terminal branches as the pontile arteries. Wilson and Winkelman [3] suggested that the increased pressure in the cranial cavity was sufficient to force the pons against the base of the skull and thus

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1. Attwater, H. L.: Pontine Hæmorrhages, Guy's Hosp. Rep. **65**:339, 1911.

2. Greenacre, P.: Multiple Spontaneous Intracerebral Hemorrhages, Bull. Johns Hopkins Hosp. **28**:86, 1917.

3. Wilson, G., and Winkelman, N. W.: Gross Pontile Bleeding in Traumatic and Nontraumatic Cerebral Lesions, Arch. Neurol. & Psychiat. **15**:455 (April) 1926.

4. Rosenhagen, H.: Pons-und Haubenblutungen als Komplikationen von Tumoren des Grosshirns, Deutsche Ztschr. f. Nervenh. **127**:27, 1932.

5. Moore, M. T., and Stern, K.: Vascular Lesions in the Brain Stem and Occipital Lobe Occurring in Association with Brain Tumors, Brain **61**:70, 1938.

to cause disturbances of circulation in the small branches issuing from the lateral and posterior surfaces of the basilar artery. Moore and Stern [5] expressed the opinion that sudden changes in the pressure relation between the supratentorial and the infratentorial spaces led to disturbances of the circulation in the rostral end of the basilar artery and that arterial congestion together with a rise in systemic pressure was the predisposing factor in hemorrhages into the pons.

Our interest in this problem arose after studying the following case.

REPORT OF A CASE

A white woman aged 68 was admitted to the Duke Hospital on Aug. 17, 1937, complaining of stomach trouble. The past history was of interest only in that she had had a goiter for ten years. The marital and family histories were of no importance in the present illness. Two months prior to admission she began to complain of progressive epigastric discomfort after meals, followed by nausea and vomiting. She had lost 30 pounds (13.6 Kg.) in weight during this time.

Physical Examination.—The patient was emaciated, ill and drowsy. The pupils reacted slowly to light and in accommodation, and the fundi showed haziness of the margins of the disks. Neurologic examination otherwise gave normal results. The heart was not enlarged. The blood pressure was 145 systolic and 105 diastolic.

The laboratory findings were within normal limits, except that the spinal fluid was grossly bloody.

Course.—The patient's condition remained unchanged for two days, when generalized spastic paralysis was noted; this was followed by death in three hours.

Autopsy.—There was subdural hemorrhage of approximately 100 cc. of liquid and clotted blood over the left frontal region. The margins of the hematoma showed early organization. In the insula, just outside the lenticulate nuclei, was another hemorrhage, measuring 2 cm. in diameter. The pons was the site of multiple fresh hemorrhages extending through the central portion (fig. I, *1* and *2*). Examination otherwise revealed adenocarcinoma of the stomach, with metastases in the liver and lungs. There was no evidence of tumor embolism in the vessels of the brain.

It seemed probable that the pressure caused by the subdural hematoma was sufficient to force the pons into the foramen magnum and produce the pontile hemorrhages by mechanical disruption of brain tissue.

EXPERIMENTAL STUDIES

An attempt was made to produce an intracerebral space-consuming mass which would compress the brain and at the same time place the cranial contents in a state of absolute anemia. A modification of the method proposed by Eyster, Burroughs and Essick [6] was used.

6. Eyster, J. A. E.; Burrows, M. T., and Essick, C. R.: Studies on Intracranial Pressure, J. Exper. Med. **11**:489, 1909.

Method.—Four large mongrel dogs of both sexes were anesthetized with ether by the inhalation drop method, and an opening, approximately 5 cm. in diameter, was trephined in the skull over the right parietal lobe. A small rubber balloon was attached by a T tube to a syringe and a mercury manometer and was placed in the subarachnoid space over the parietal lobe. The femoral artery was cannulated, and the systemic blood pressure was recorded every fifteen seconds during the experiment.

By injection of physiologic solution of sodium chloride into the rubber balloon, the intracranial pressure, as recorded by the mercury manometer, was abruptly

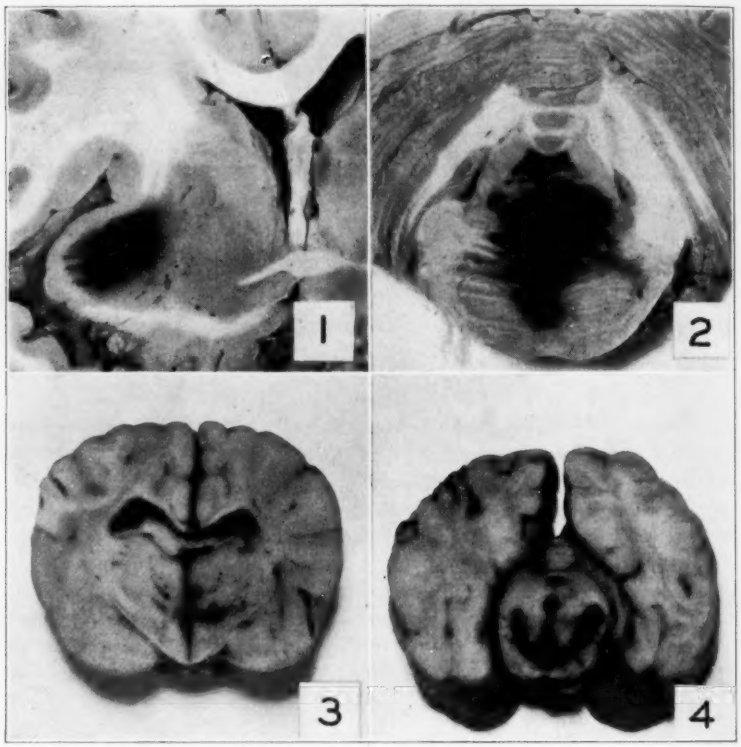

Fig. I.—*1* is a transverse section of human brain through the mamillary bodies, showing the hemorrhage in the insula; *2*, a transverse section of human brain through the cerebellum and pons, showing pontile hemorrhages; *3*, a transverse section of the brain of an animal of the experimental group at the level of the mamillary bodies, showing hemorrhages into the basal ganglia, and *4*, a transverse section through the cerebellum and medulla of the brain of an animal of the experimental group, showing hemorrhages.

raised to 100 mm. of mercury above the systolic blood pressure and left at that level for periods varying from one to three minutes. The pressure in the balloon was then allowed to fall back slowly to the resting level (from 0 to 10 mm. of mercury). This procedure was repeated at intervals of ten or twenty minutes. After from three to six such elevations of intracranial pressure the animal was

killed, if the medullary centers had not already failed to regain function. After the first period of anoxemia, the blood pressure usually attempted to parallel the intracerebral pressure; in order to keep the brain anoxemic it was necessary constantly to raise the intracerebral pressure. The blood pressure occasionally exceeded 300 mm. of mercury. The rather characteristic reactions of animals subjected to this procedure have been carefully noted by Eyster, Burroughs and Essick.

In order to render the brain completely anoxemic, control experiments (group 1) were made independent of the traumatic element. Eight dogs of the same type used in the experimental group were similarly anesthetized, and the third and fourth lumbar laminas were resected. A glass cannula was tied into the subarachnoid space and connected to a mercury manometer and a large syringe by a T tube. The pressure in the subarachnoid space was maintained at the required level by the injection of physiologic solution of sodium chloride into the cannula. The same pressure relations and time intervals were used here as in the experimental group.

In order to rule out changes produced by ether anesthesia and artefacts produced by technical preparation of the material, another group of control experiments (group 2) were performed. Four dogs of the same type used in the rest of the experiment were killed by inhalation of ether.

Autopsy was performed in each case immediately after death or after the animal had been killed, and the brain placed in dilute solution of formaldehyde U. S. P. (1:10). Representative blocks were embedded in paraffin, cut at 8 microns and stained with hematoxylin and eosin.

Results in Experimental Groups.—Gross Observations: All animals in which the intracranial pressure had been raised by inflating a balloon over the parietal cortex showed hemorrhages into the brain tissue. A few petechiae were seen in all the brains, distributed throughout the parietal cortex at the position of insertion of the balloon. All showed areas of hemorrhage into the pons and medulla, which varied from pinpoint-sized flecks to areas as much as 0.5 cm. in diameter. In 2 instances small cerebellar hemorrhages were present, and in 1 involvement of the basal ganglia was noted (fig. I, *3* and *4*).

Microscopic Observations: The tissue of the pons and medulla, which grossly seemed normal, showed evidences of severe injury. Separation of nerve and glia fibers, with collections of fluid, was seen. In some places small collections of red cells were seen lying in otherwise uninjured brain tissue. No effort was made to study carefully the cytologic changes of the neurons, as these have been elaborately studied by Pike, Stewart and Guthrie;[7] Heymans and Bouckaert;[8] Gildea and Cobb,[9] and others, but it was obvious that these structures had undergone marked changes. The smaller hemorrhages were usually perivascular and occurred almost as frequently around veins as arteries (fig. II, *5*). Usually they were unaccompanied by any remarkable degree of injury, either to the wall of the vessel or to the surrounding brain tissue, although in some instances there seemed to have been a centripetal compression of the nerve tissue in the immediate vicinity of the vessel. The large hemorrhages were usually present in the vicinity

7. Pike, F. H.; Guthrie, C. C., and Stewart, G. N.: Studies in Resuscitation, J. Exper. Med. **10**:490, 1908.

8. Heymans, C., and Bouckaert, J. J.: Sur la survie et la réviviscence des centres nerveux encéphalo-bulbares, Compt. rend. Soc. de biol. **119**:324, 1935.

9. Gildea, E. F., and Cobb, S.: The Effects of Anemia on the Cerebral Cortex of the Cat, Arch. Neurol. & Psychiat. **23**:876 (May) 1930.

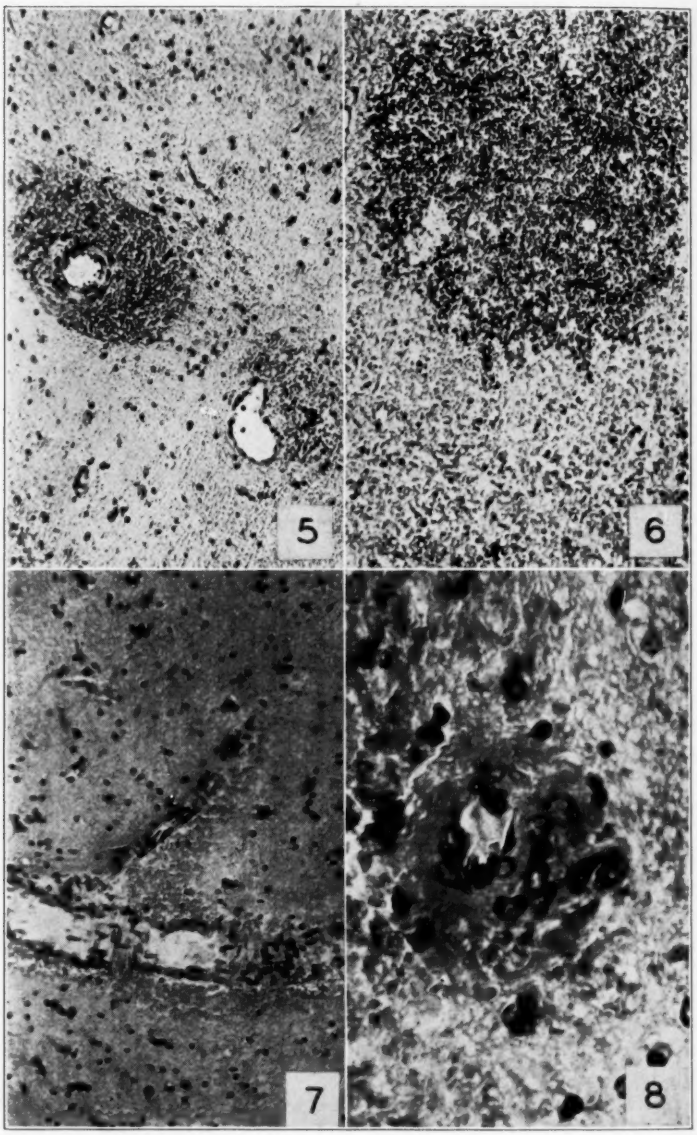

Fig. II.—*5* is a section of the medulla of an animal of the experimental group, showing hemorrhages around a small artery and a small vein; *6*, a section of the pons of an animal of the experimental group, showing an extravasation of red cells into the tissue; *7*, a section of the medulla of a control animal, showing perivascular hemorrhage, and *8*, a section of the pons of an animal of the experimental group, showing injury to the arterial wall in an area of hemorrhage.

of vessels of fair size, although a few extravasations were present in which serial sections failed to reveal a large vessel from which they might have arisen (fig. II, *6*). Actual destruction of a considerable amount of brain tissue was evident in the neighborhood of these extravasations. In some areas the disruption was so complete that the actual structure was not evident. The walls of the vessels in such areas were obviously injured; the nuclei were pale, and the muscular layer was edematous (fig. II, *8*).

Results in Control Experiments.—Because of the similarity of the changes both in the animals in which brain tissue had been exposed to complete acute anoxemia and in those in which death had been produced by inhalation of lethal amounts of ether, the pathologic observations will be described together.

Gross Observations: The vessels of the meninges and throughout the brain showed an extreme amount of dilatation in both groups of animals. No obvious hemorrhages could be made out with the naked eye.

Microscopic Observations: The brain tissue was not remarkable in appearance. Rarely, a minute area of edema in the glial network could be made out. In infrequent areas a few red cells could be seen lying free in the brain tissue. Accumulations of red blood cells in the perivascular spaces were seen infrequently, and occasionally moderate quantities (fig. II, *7*). Significant changes appeared no more often and in no greater proportions in the animals subjected to cerebral ischemia than in those in which death had been produced by inhalation of lethal amounts of ether.

COMMENT

Since Westphal and Bär [10] observed small extravasations of blood into the perivascular spaces of rabbit brains to which the blood supply had been temporarily severely diminished, the role of anoxemia in the production of cerebral hemorrhage of all types has been repeatedly stressed.[11] Numerous investigators have studied the effects of acute anemia on the brain and have made no mention of the presence of perivascular bleeding, although Wolff,[12] using a transparent plate in the skull of cats, had seen red cells pass through the intact wall of small pial vessels in brains previously made anemic.

It seems unlikely that anoxemia played any part in the production of the pontile hemorrhages observed in the animals in which the

10. Westphal, K., and Bär, R.: Ueber die Entstehung des Schlagenfalles, Deutsches Arch. f. klin. Med. **151**:1, 1926.

11. Bohne, C.: Beiträge zum Problem der apoplektischen Hirnblutung, Beitr. z. path. Anat. u. z. allg. Path. **78**:260, 1927. Hiller, F.: Zur Pathogenese der apoplektischen Hirnblutung, Verhandl. d. deutsch. Gesellsch. f. inn. Med. **42**:202, 1930. Ricker, G.: Die Entstehung der pathologisch-anatomischen Befund nach Hornerschütterung in Abhängigkeit von Gefässnervensystem des Hirnes, Virchows Arch. f. path. Anat. **226**:180, 1919. Friedmann, M.: Ueber einen weitern Fall von nervösen Folgezuständen auch Gehirnerschütterung mit Sectionsbefund, Deutsche Ztschr. f. Nervenh. **11**:376, 1897.

12. Wolff, H. G.: The Cerebral Circulation, Physiol. Rev. **16**:545, 1936.

intracranial pressure had been elevated by means of an inflated balloon in the cranial cavity, since comparable cerebral anemia without trauma failed to produce any significant vascular lesions.

It seems probable that vertical compression of the brain tends to cause herniation of the pons and medulla into the foramen magnum. This herniation causes lateral compression of the pontile structures, with consequent elongation of the pons in the longitudinal axis.[13] The change in the normal configuration of the pontile tissue places considerable stress on the small vascular units of this tissue, particularly the long central branches of the basilar artery at the positions of relative fixation, such as the origin of branches and the junctions of venous channels.

We are inclined to believe that arterial necrosis plays no part in the production of these hemorrhages, as injury to the arterial wall is evident only in instances in which huge extravasations of blood are present.[14] Extravasations around veins are not infrequent in these animals, and this observation alone, which has been noted [5] in pontile hemorrhages in man, should serve to rule out arterial spasm and intravascular pressure as causative factors.

CONCLUSION

Pontile hemorrhages, which resemble those seen in patients with space-consuming intracranial lesions, can be produced in the dog by mechanical compression of the cerebral cortex.

Anoxemia as an etiologic factor can be ruled out. It seems likely that mechanical stretching, with subsequent rupture of units of the vascular bed, is responsible for the hemorrhages.

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13. This can be illustrated simply by lateral constriction of a tube of tooth paste which is open at both ends.

14. Bouman, L.: Hemorrhage of the Brain, Arch. Neurol. & Psychiat. **25**:255 (Feb.) 1931.

ALTERATIONS IN RESPONSE TO VISUAL STIMULI FOLLOWING LESIONS OF FRONTAL LOBE IN MONKEYS

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The regions of the frontal lobe which lie rostral to the excitable motor areas are generally associated with the so-called higher integrative processes of the cerebral cortex. In man structural alteration in these regions results in changes such as loss of immediate memory and alterations in personality and behavior. In the monkey extirpation of these areas (fields 8, 9, 10, 11 and 12 of Brodmann;[1] fig. 1) is followed by similar behavioral changes, without motor paresis. Thus, Ferrier[2a] (pages 231-232) noted that such animals

> instead of, as before, being actively interested in their surroundings, and curiously prying into all that came within the field of their observation, remained apathetic, or dull, or dozed off to sleep, responding only to the sensations or impressions of the moment, or varying their listlessness with restless and purposeless wanderings to and fro. While not actually deprived of intelligence, they had lost, to all appearance, the faculty of attentive and intelligent observation.

Hitzig[3] ascribed the same type of behavior in dogs deprived of frontal areas to "mental deterioration." The dogs of Goltz[4] exhibited great irritability and restlessness and "a fixed and stupid expression of the eyes and inability to fix the gaze." The monkeys of Bianchi[5] after bilateral ablation of the frontal lobes were listless, lacked initiative and did not recognize objects seen.

From the Laboratory of Physiology, Yale University School of Medicine.

This work was aided by a grant from the Fluid Research Funds, Yale University School of Medicine.

1. Brodmann, K.: Vergleichende Lokalisationslehre der Grosshirnrinde in ihren Prinzipien dargestellt auf Grund des Zellenbaues, Leipzig, J. A. Barth, 1909; reprinted, 1925.

2. Ferrier, D.: (*a*) The Functions of the Brain, London, Smith, Elder & Co., 1876; (*b*) Experiments on the Brains of Monkeys, Proc. Roy. Soc., London **23**: 409, 1875.

3. Hitzig, E.: Physiologische und klinische Untersuchungen über das Gehirn: Alte und neue Untersuchungen über das Gehirn, Berlin, A. Hirschwald, 1904, pt. 2.

4. Goltz, F.: Ueber die Verrichtungen des Grosshirns, Arch. f. d. ges. Physiol. **34**:450, 1884.

5. Bianchi, L.: The Mechanism of the Brain and the Function of the Frontal Lobe, translated by J. H. MacDonald, New York, William Wood & Company, 1922.

In all these descriptions of changes following injury to the frontal lobe it is interesting that alterations in response to visual stimuli were so often noted. While restlessness, and the like, was reported only after bilateral lesions, unilateral ablation of the same areas has caused an apparent failure to recognize objects in the contralateral homonymous visual field (Hitzig,[3] Minkowski,[6] Bianchi [7]). In the experiments to be described, observations have been made on the nature of this "visual" defect and its relation to area 8 of the frontal cortex.

METHOD

Rhesus (Macaca mulatta) and mangabey (Cercocebus torquatus atys) monkeys were used. Normal performance was observed in various test situations over a

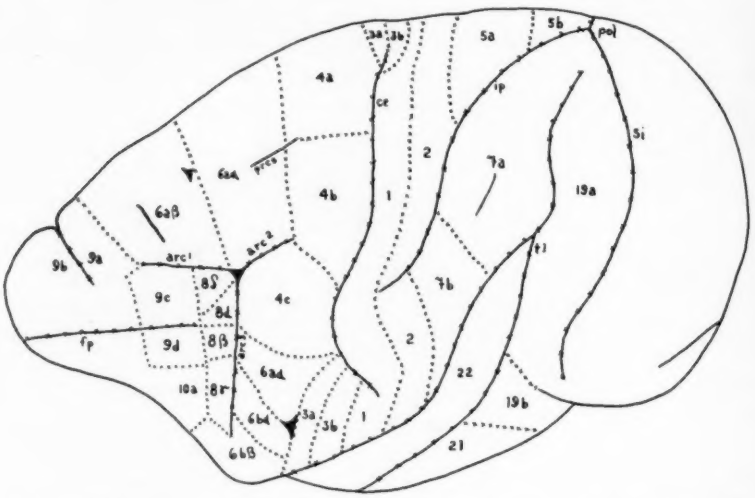

Fig. 1.—Diagram of the monkey's left hemisphere, showing Brodmann's numerical designation of cortical areas as modified by the Vogts (Allgemeinere Ergebnisse unserer Hirnforschung, J. f. Psychol. u. Neurol. **25**:279, 1919).

period, after which cortical extirpations were made and the test situations repeated. A detailed account of the apparatus used for testing the fields of vision will be given under the appropriate heading. Cortical extirpations were made with aseptic technic (Fulton and Keller [8]) and detailed observations recorded thereafter.

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6. Minkowski, M.: Zur Physiologie der Sehsphäre, Arch. f. d. ges. Physiol. **141**:171, 1911.

7. Bianchi, L.: The Functions of the Frontal Lobes, Brain **18**:497, 1895.

8. Fulton, J. F., and Keller, A. D.: The Sign of Babinski: A Study of the Evolution of Cortical Dominance in Primates, Springfield, Ill., Charles C. Thomas, Publisher, 1932.

PRELIMINARY OBSERVATIONS

In the course of investigations on the functions of the frontal lobes it was early noted that monkeys from which one entire frontal lobe had been removed did not appear to see objects in the contralateral field of vision. Food placed in the cages was ignored on that side, but the animals quickly reached for the same food when placed in the ipsilateral visual field. The blink response to threat was also absent on the contralateral side. A normal monkey, if threatened by a sudden movement of the examiner's hand, will respond by blinking and often also by jumping. After removal of a frontal lobe there is no such blink reaction to stimuli in the contralateral visual field, while the response from the ipsilateral field continues normal; also, if the animal's head is held, a peanut or a bit of sugar suspended on a string can be brought into the fields of vision from the side. On the normal side the eyes perceive the object and follow it from the periphery inward, but on the abnormal side no sign of recognition occurs until the midline is reached, when the eyes "pick up" the object and again follow it. By none of these tests could the defect following lesions of the frontal lobe be distinguished from the true hemianopia which follows amputation of one occipital lobe. The defect from frontal lesions is not a true hemianopia, however, since it is only transient, appearing immediately after operation and gradually disappearing during the succeeding weeks. Peripheral vision is the last to return. The sequelae of frontal lobe lesions also differ from those of occipital lesions, since total blindness does not result from bilateral lesions.

CORTICAL AREA RESPONSIBLE FOR VISUAL CHANGES

By making a series of small discrete lesions involving only the gray matter of the frontal cortex, it was possible to identify an isolated area ablation of which was constantly followed by this unilateral visual defect; extirpation of no other part of the frontal lobe had any influence on the visuomotor performance of the animal. Unilateral removal of areas 4 and 6 resulted in contralateral hemiparesis, but without alteration in response to visual stimuli. After ablation of the frontal association fields (areas 9, 10 and 11) the monkeys also see and recognize objects in the full extent of their visual fields (Kennard and Ectors [9]). On the other hand, extirpation of area 8, the small region lying inside the curvature of the arcuate sulcus (fig. 1), was invariably followed by a failure to respond in the normal manner to objects placed in the contralateral visual field. Area 8 is the region known to be responsible for conjugate deviation of the head and eyes (Hitzig,[3] Leyton

9. Kennard, M. A., and Ectors, L.: Forced Circling in Monkeys Following Lesions of the Frontal Lobes, J. Neurophysiol. **1**:45 (Jan.) 1938.

and Sherrington,[10] Levinsohn[11]). Furthermore, the defect always occurred in the same animals in which after operation there was deviation of the head and eyes toward the side of the lesion; in no case has the defect been present in an animal in which deviation of the head and eyes did not also appear. However, the latter symptoms, also transient, disappear some time before the disappearance of the "visual" defect.

There is a specific syndrome which appears after ablation of this region (Kennard and Ectors[9]); there is no paresis; gait, posture and fine movements of prehension are all normal, but the head and eyes are turned toward the side of the lesion and the animal circles continuously in the same direction. In such animals movements of the eyes and head are possible in the opposite direction (i. e., away from the side of the lesion), but the tendency is to turn toward the ipsilateral side. These monkeys fail to respond to objects on one side; in addition, although there is no detectable paresis, the contralateral hand is used less often for fine movements than is the normal ipsilateral hand. All these symptoms gradually disappear after a variable interval following operation. The head and eyes return first to the normal position, usually within two to three weeks, and the circling then gradually lessens. The visual field defect often endures long after the deviation of the head and eyes has disappeared, and the use of the sound hand in preference to the other persists still longer; a tendency to circle, particularly when the animal is excited or emotionally stimulated, continues indefinitely, although it becomes must less prominent in later weeks.

EXAMINATION OF THE VISUAL FIELDS

Accurate delimitation of the fields of vision in monkeys is obviously impossible, but various clinical methods of field examination have proved useful. The absence of blink in response to threat and the inability to pick up objects placed in one half of the visual field gave convincing evidence—as it had to Hitzig, Bianchi and Minkowski—that visual stimuli from this homonymous field did not evoke the normal response. Attempts to fix the head of the animals was impracticable because the monkeys failed to cooperate. With the apparatus which was evolved, however, existing defects could be well demonstrated without restraining an animal or in any way altering its behavior.

The monkey, kept in cage *A* (fig. 2), was fed daily when let into compartment *B*; from *B* a narrow passage, *C*, led off and was blocked only by a perpendicular

10. Leyton, A. S. F., and Sherrington, C. S.: Observations on the Excitable Cortex of the Chimpanzee, Orang-Utan and Gorilla, Quart. J. Exper. Physiol. **11**:135 (July) 1917.

11. Levinsohn, G.: Ueber die Beziehung der Grosshirnrinde beim Affen zu den Bewegungen des Augens, Arch. f. Ophth. **71**:313, 1909.

bar, *D*, to prevent the escape of the animal. The sides of chamber *C* were opaque, and the passage was just wide enough to permit the animal to stand in it. Food was always placed on the tray, *E*, and was reached for by the monkey from the passage. Thus, the image of small bits of food placed to either side fell in one-half the retinal field only. Normal monkeys were fed daily in this manner over a period of two weeks preceding operation. Bits of food—banana, peanuts or sugar—were arranged in various ways on the board. The animal was then allowed into the passage, and the way in which it took its food was observed and recorded. Records show: (i) the hand used for picking up objects in the various positions and (ii) the order in which objects were removed from the various positions. Many arrangements of food were made. Thus, one or two bits only might be put in the periphery or center. For purposes of recording, however, two setups only were employed. These were found by experience to demonstrate performance most effectively. In the "six choice setup" objects were placed in a semicircle on six spots marked on the tray—the inner semicircle of dots in figure 2 *E*. In the "eight choice setup" food was placed in two groups of four spots—to either side on the tray, as shown by the solid dots in figure 2 *E*. In both these arrangements normal performance of the monkeys showed consistent characteristics, which were altered by ablations of various cortical areas.

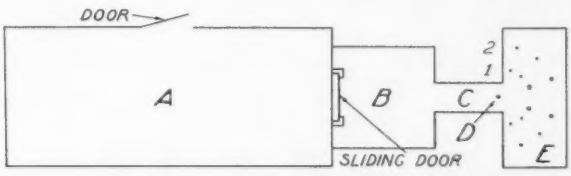

Fig. 2.—Plan of apparatus used for testing visual performance in monkeys. *A* represents the large cage; *B*, the smaller cage: *C*, the corridor into which the animal can walk; *D*, the bar to prevent escape of the monkey, and *E*, the tray on which food is arranged in semicircles.

PERFORMANCE OF NORMAL MONKEY

The normal monkey confronted by these test situations behaves much as would a hungry man in like circumstances. It gets the food to its mouth as rapidly and as easily as possible. The tendency is to use either hand and to pick up the most available objects first.

Each animal was tested four times daily; i. e., food was placed in the six positions *A* to *F* (fig. 3) four times. At each trial, the hand (left or right) used in each position and the order of choice (i. e., first choice = 1; second choice = 2) were recorded. The average of the four numbers for each position was then taken and is recorded on the graph. The lower scores (positions *B* and *E*) are thus the positions from which food was taken first. Positions *C* and *D* were less often chosen first, because the central bar (*D*) restrained movement of the animal. The two lateral positions (*A* and *F*) had the highest scores, indicating that they were chosen last because of the difficulty in reaching to the side from the restraining corridor.

To date, 8 monkeys have been used in this series—6 mangabeys and 2 macaques. To establish normal standards, each animal, after a

few preliminary days, during which it became accustomed to the apparatus, was tested on ten successive days in both "six choice" and "eight choice setups." In order to simplify and condense the presentation of the material, the graphs reproduced here represent findings from

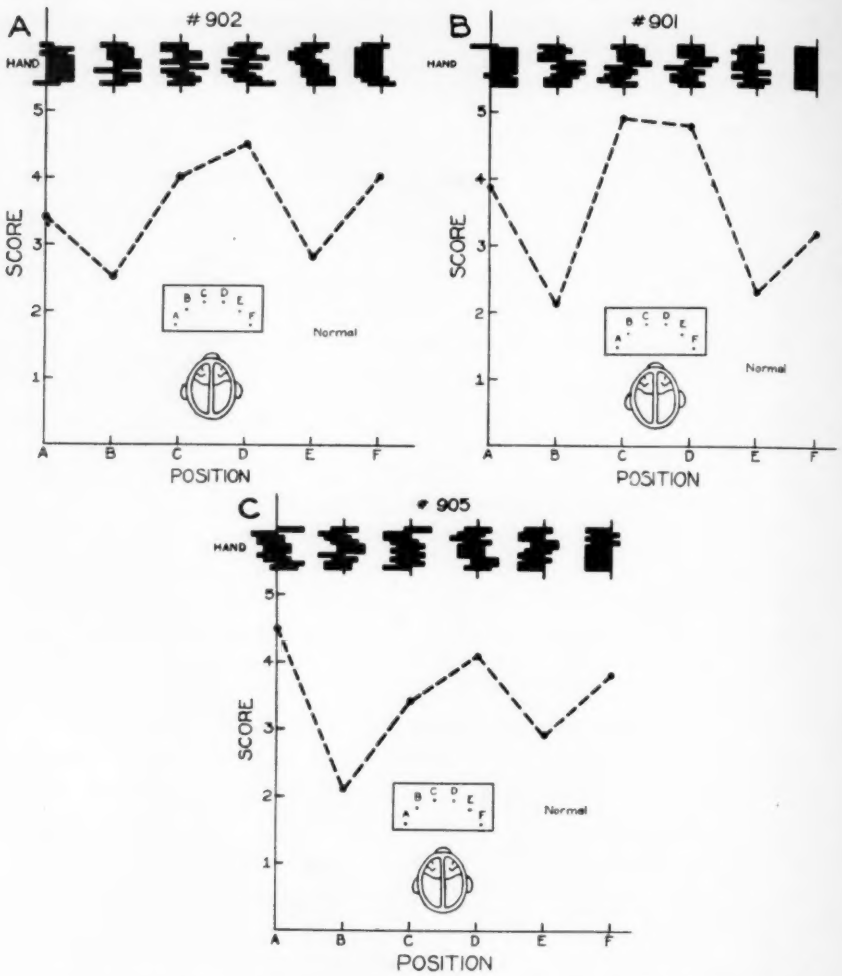

Fig. 3.—Diagrams of performance of 3 normal monkeys. The position of the monkey and food is shown in the inset. The order of choice of food in each position (*A-F*) is indicated by the graph (average of four trials daily, for ten days). Low scores indicate first choice, and high scores, later choices (see text, page 1157). The hand used in each position is shown above; the use of the left hand is recorded in each position to the left of each ordinate, and vice versa.

the "six choice setup" only. Changes of the same nature were shown in all other test situations used. On the same charts the hand used

in each position is recorded above the graph. Each block to the right of each ordinate represents the use of the right hand in that position, and vice versa. For the normal animals the tests on ten days are shown one above the other. It can be seen that to the left of the animal the right hand was most often used, and to the right side the left hand.

In the charts of postoperative performance, representation is made in the same way; the preoperative curve is shown in dotted line for comparison with the postoperative curve, in solid line. The postoperative records are for single days only, since performance changed rapidly in some instances. After operation, tests were made on these animals at first daily, or every other day, but later, when symptoms changed less rapidly, weekly or monthly records only were necessary.

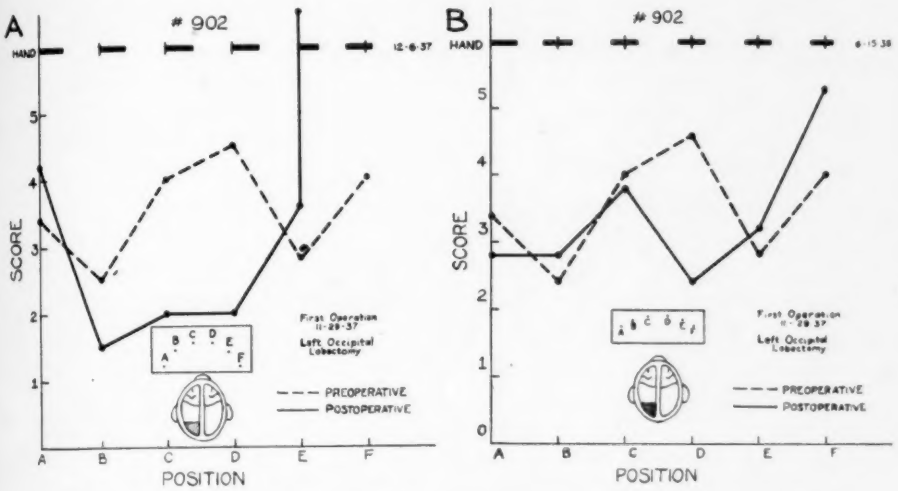

Fig. 4.—Diagram of performance of a monkey (no. 902) following left occipital lobectomy (the normal performance of the same animal is shown in figure 3 *A*). After operation the right side of the field was ignored. The hands were used as before operation.

UNILATERAL OCCIPITAL LOBECTOMY

In using this technic it was evident that the removal of one occipital lobe, which produces a true homonymous hemianopia, is accompanied by permanent and consistent changes in performance.

EXPERIMENT 1.—The left occipital lobe was removed on Nov. 29, 1937, from a mangabey monkey (no. 902), the normal preoperative data for which are recorded in figure 3 *A*. The postoperative hemianopia in the right visual field is shown in figure 4 *A* by the failure to pick up objects in the far right field of vision and by the higher scores made in the more central parts of this side as compared with the preoperative record. The use of the two hands was the same as before operation. Tests through successive months showed that the hemianopia continued (fig. 4 *B*, June 15, 1938) although performance improved slightly when the animal learned

to expect food in every direction on the tray and was seen to reach and feel for the food it could not see on the hemianopic side.

UNILATERAL ABLATION OF AREA 8

Immediately after unilateral ablation of area 8, the behavior of a monkey in response to visual stimuli cannot be ordinarily distinguished from that of an animal with true hemianopia. In every test the contralateral field of vision seemed unresponsive to stimuli.

EXPERIMENT 2.—Placed in the test situation just described, a mangabey (no. 901) responded in the normal manner, both in the order of choice and in the hand used for various positions in the semicircle (fig. 3 *B*). On Nov. 9, 1937, area 8 was removed from the left hemisphere. Figure 5 *A* shows the resultant change when tested on November 11, two days later. Objects in the right field of vision were ignored in the peripheral position; they were chosen last in the more central position on that side, exactly as in true hemianopia. In addition, there was a modification in the choice of hands used, which does not appear after occipital lobectomy. The ipsilateral hand was used almost entirely. Thus, the left hand was used for objects far to the left of the animal—a maneuver mechanically much more difficult than if the right hand were employed, and one seldom used by normal animals.

These animals show no motor paresis which can account for such performance. In fact, until this test was devised there had been no suggestion of any motor alteration in limb performance following discrete unilateral ablation of area 8 (Kennard and Ectors [9]); the gait, posture and fine motor acts, such as "grooming" or picking up small objects, *may* be executed in these animals by the contralateral extremities exactly as they are by the ipsilateral ones. Yet there is always a tendency to use the ipsilateral hand in preference to the contralateral. Both the visual and the motor deficit disappeared (fig. 5 *B*) four months after operation. Subsequent removal of the frontal association areas at a second operation (fig. 5 *C*) did not affect performance in any way.

EXPERIMENT 3.—Another mangabey (no. 905) also had normal performance (fig. 3 *C*) before operation. On Oct. 22, 1937, the right frontal association field (areas 9-12) together with area 8 was removed. The usual deficit resulted, as shown in figure 6 *A*, taken from a record made six days after operation. The hand also was affected, since in this instance the contralateral hand was not used at all for this skilled performance although there was no trace of motor paresis. By April 18, 1938, both hand and eye performance had returned to normal (fig. 6 *B*). On May 17, 1938, the left area 8 and frontal association areas were removed, and there followed failure to respond to visual stimuli on the right and a marked tendency to use the left hand (fig. 6 *C*) instead of the right.

LESIONS OF THE MOTOR AREAS

The monkey with true motor paresis produced by a lesion of area 4 or 6 (causing motor weakness of the opposite extremities) shows a different type of performance with these visuomotor tests. Such an

animal never fails to pick up equally well all objects in the two fields of vision. If because of paresis of a hand he cannot reach an object he will demonstrate in every way by reaching with the normal hand that he sees the unattainable.

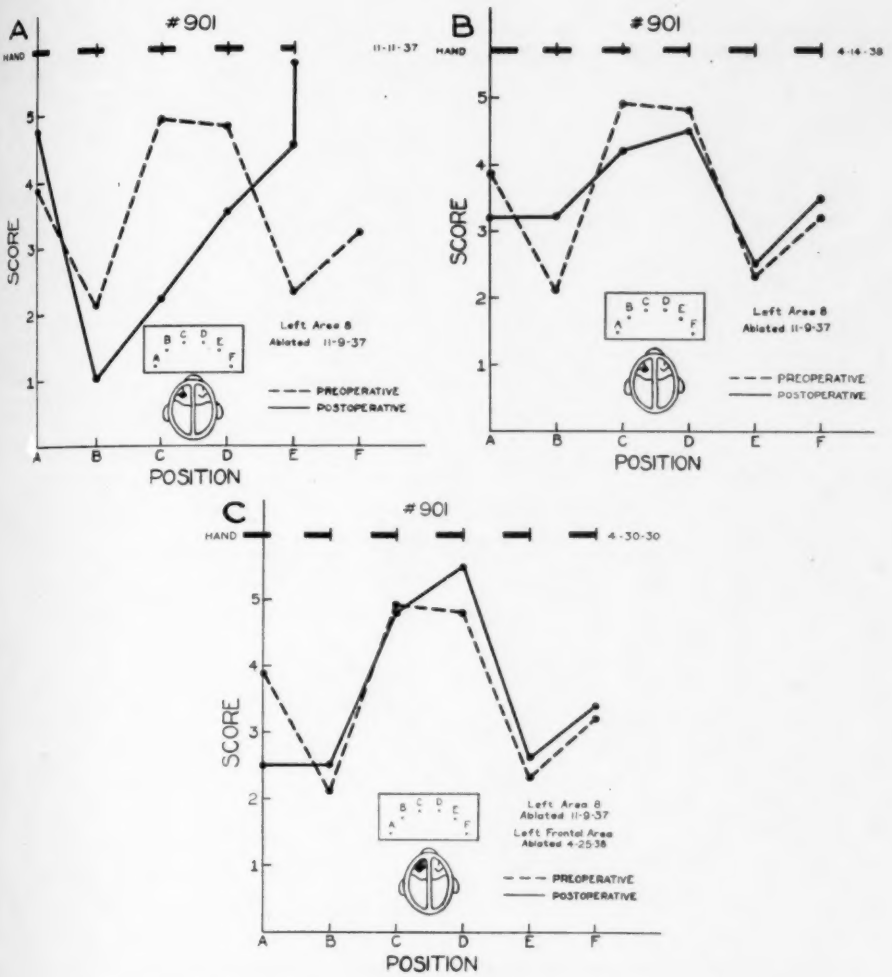

Fig. 5.—Diagram of performance of monkey no. 901 (normal performance shown in figure 3 *B*) immediately following ablation of the left area 8, showing predominant use of the left hand and ignoring of objects in the right field of vision (*A*). Five months later performance had returned to normal (*B*). Subsequent ablation of areas 9-12 had then no effect on this performance (*C*).

RESPONSE TO VISUAL STIMULI FOLLOWING SIMULTANEOUS BILATERAL ABLATION OF AREA 8

If, then, unilateral extirpation of area 8 gives a homonymous defect whereby objects in this field of vision are ignored, the performance of

an animal after simultaneous bilateral extirpation of area 8 invites attention. Such an animal immediately after operation is not blind, since at times it follows a light or moving objects with its eyes; usually, however, visual perception seems absent. For the first few days after

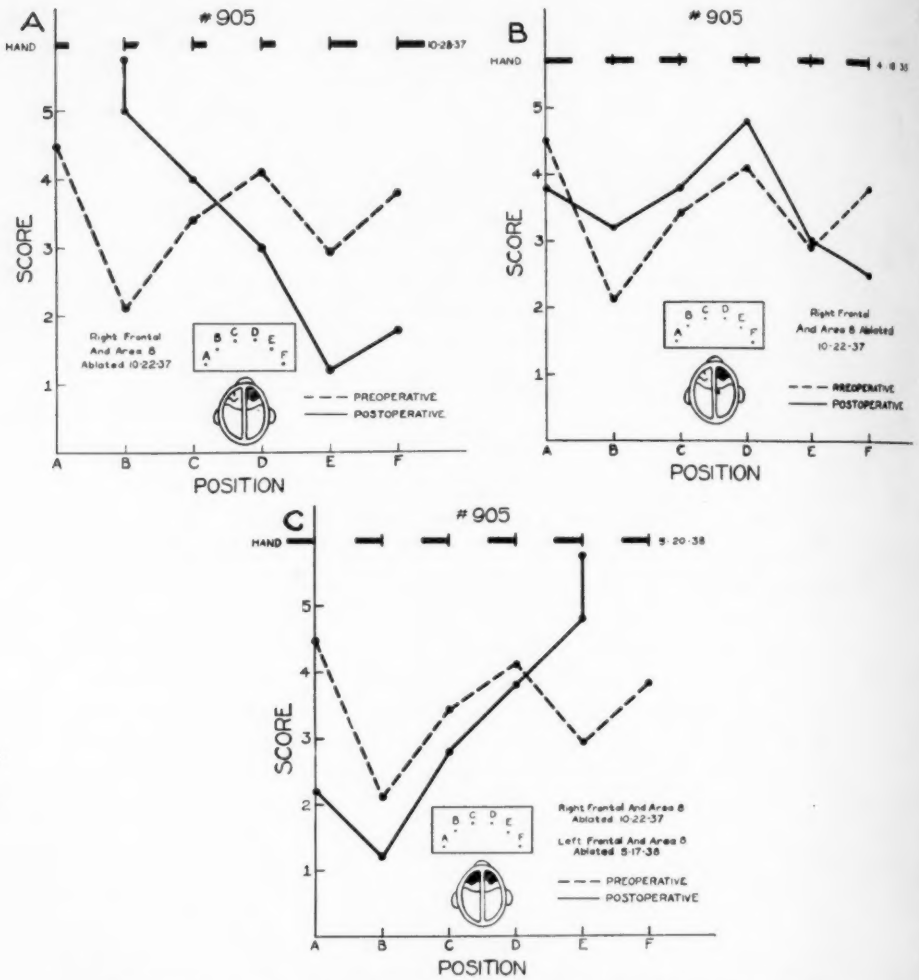

Fig. 6.—Diagram of performance of a monkey, no. 905 (normal performance shown in figure 3 *C*), after ablation of areas 8-12 on the right, showing immediately after operation (*A*) predominant use of the right hand and ignoring of objects in the left visual field; recovery after five months (*B*), and then, after removal of areas 8-12 on the left, ignoring of the right visual field and use of the left hand (*C*).

operation these monkeys sit motionless in the cage; food placed before them may be ignored; it may be reached for and held indefinitely, or

it may be dropped to the floor. Objects are sometimes put to the mouth, but inedible material is as likely to be chewed as food—behavior never seen in a normal animal, which is always ready and able to discriminate between its likes and dislikes. Chewing is also stereotyped; food in the mouth may be chewed for a long time but not swallowed, or, once the food is swallowed, the animal may continue mastication although the mouth is empty; perseveration is also seen in hand performance. When the animals are stimulated into action they will often start to walk and continue slowly and mechanically, at times walking into large objects as if completely blind, but at other times avoiding objects in the visual field; if their attention is attracted by sound or by visual stimulus, they may walk toward the stimulus, then stop part way and stand immobile.

The facial expression of these animals is peculiar, for they do not often blink spontaneously, and blinking in response to threat is difficult to elicit or is absent. For the first week or ten days after operation they move little; often they have to be fed by pouring liquid into the mouth, but gradually they begin to reestablish former habits of eating and moving; they then move more rapidly and respond in more normal manner to all types of stimuli. The stereotypy and perseveration of performance persist indefinitely; the animals become extremely hyperactive, moving incessantly in a purposeless manner and often displaying excessive emotional reaction to stimuli that in a normal animal would fail to evoke such a response.

GENERAL COMMENT

After ablation of area 8 from one frontal lobe monkeys exhibit a transient defect in response to visual stimuli in the homonymous visual field contralateral to the extirpated cortical area. This is similar to the "hemianopia" described by many authors in dogs and monkeys following frontal extirpations of all tissue rostral to the excitable areas (Bianchi,[12] Goltz,[4] Hitzig,[13] Kennard and Ectors[9]). Objects brought into the contralateral visual fields of these animals are ignored in the same way they are by hemianopic animals after removal of one occipital lobe. The defect after frontal extirpations is not a true hemianopia, since a bilateral lesion does not produce total blindness. It does, however, cause some alteration in response to visual stimuli, since the animals either ignore objects or do not appear to appreciate their significance. A similar alteration of hand performance occurs

12. Bianchi (footnotes 5 and 7).

13. Hitzig, E.: Untersuchungen über das Gehirn, Berlin, A. Hirschwald, 1874; footnote 3.

after lesions of area 8, which is not present in the animal after occipital lobectomy. Although there is no detectable paresis, the contralateral hand is often not used, or, when used, the response is incomplete or ineffective. Stereotyped performance and perseveration of movement are prominent in walking, chewing or prehension following bilateral lesions. They decrease with time, as the animal seems to reacquire purposeful movements.

The relation of the alteration in response to visual stimuli to the paresis of conjugate deviation of the eyes cannot be fully analyzed from the available data. The fact that the visual defect and paresis of conjugate deviation of the eyes always appear in the same animal makes one suspect a functional relationship. It is certain that the "visual" deficit is not an artefact due to change in position of the head and eyes, for it often endures after the position of the head and eyes has returned to normal. Also close observation indicates that the defect is homonymous, regardless of the position of the eye at the moment of examination. Binocular vision must depend in part on proprioceptive afferent impulses from extraocular muscles for recognition of space relationships, and since, in the presence of conjugate deviation of the eyes, the relationships of these proprioceptive impulses must be altered, it is conceivable that normal recognition of objects might be changed. If this were the case, however, the relationship of objects in both halves of the fields of vision should be distorted, and one would not expect a homonymous field defect. The abnormality of behavior in response to visual and to tactile stimuli seems to be of the same order and resembles that of the apraxic patient. Similar unilateral visual changes have also been described by Bard [14] in human subjects with hemiparesis.

In the monkey this syndrome can be produced by lesions involving the gray matter only, when the afferent cortical paths to the parietal and occipital lobes remain intact, as do the motor effectors. The association pathways alone must be interrupted, and with them the more complex integrative functions of the visuomotor and tactuomotor system. The general behavior of an animal or of a man with disturbances of this sort, which make him unable to respond in the normal manner to objects seen or touched, would be enough to account for the dulness, the "intellectual changes" and the general stupidity of behavior ascribed to disturbances in the frontal lobe, which on analysis may be only a failure to recognize or to respond normally to the ordinary test situations of existence.

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14. Bard, L.: De l'origine sensorielle de la déviation conjugée des yeux avec rotation de la tête chez les hemiplégiques, Semaine méd. **24**:9, 1904.

CONCLUSIONS

1. Failure of response to visual stimuli following lesions of the frontal lobe appears after ablation of area 8, but not of other regions of the frontal cortex.

2. After unilateral ablation of area 8 objects in the contralateral visual field are ignored.

3. After unilateral ablation of area 8 the resultant "visual" defect in the contralateral homonymous field cannot be differentiated from a true hemianopia except that it is transient.

4. Hand performance contralateral to a lesion of area 8 is also altered. The hand is used less often, and effective purposeful movements are not well carried out.

5. The failure to respond to objects seen and objects touched is of the same order.

6. The apparent lack of recognition of objects is due to disturbance of the more complex integrative processes of the frontal lobe, which can account for the alterations in behavior of these animals.

CONSCIOUS INABILITY TO SYNTHESIZE THOUGHT IN A CASE OF RIGHT FRONTAL TUMOR AND LOBECTOMY

ANATOMIC CONSIDERATIONS CONCERNING THE NEURONS OF INTELLECT

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For a long time information concerning the intellectual functions of the human frontal lobes was necessarily derived from patients with spontaneous frontal lesions. The tumors, infections, injuries and atrophies which formed the groundwork for these studies carried with them the inherent complication of more or less widespread damage to the brain. Within recent years, Dandy has initiated the performance of lobectomies on human beings. He has thus made possible a new and useful method for the investigation of function of the human brain.

Only 1 patient has survived bilateral frontal lobectomy long enough to permit detailed study. The study of this patient has been reported on previously.[1] The changes in the patient's behavior were massive. It is therefore of great interest to find that unilateral lobectomies produce virtually no alteration in human subjects. This fact receives emphasis from a similar striking difference between the results of unilateral and those of bilateral lobectomy in apes. The reports on unilateral lobectomies in man and experiments with apes are reviewed later in this article. The difference between the effects of unilateral and those of bilateral frontal lobectomy suggests anatomic deductions concerning the neurons of intellect, which will be considered later.

This study is part of a project the expenses of which were paid by the Diamond Jubilee Fund and the Louis Wiley Memorial Fund.

A paper incorporating this article and a report previously published in the ARCHIVES [1d] was read at the Eighty-Ninth Annual Session of the American Medical Association, Section on Nervous and Mental Diseases, at San Francisco, June 15, 1938. The discussion was published with the latter article.

1. Brickner, R. M.: (*a*) Intellectual Functions of the Frontal Lobes: A Study Based upon Observation of a Man After Partial Bilateral Lobectomy, New York, The Macmillan Company, 1936; (*b*) The Role of the Frontal Lobes in Intellectual Function: A Study Based upon a Case of Partial Bilateral Frontal Lobectomy, Psychiat. en neurol. bl. [**38**]:332, 1934; (*c*) An Interpretation of Frontal Lobe Function Based upon the Study of a Case of Partial Bilateral Frontal Lobectomy: Localization of Function in the Cerebral Cortex, A. Research Nerv. & Ment. Dis., Proc. **13**:259, 1932; (*d*) Bilateral Frontal Lobectomy: Follow-Up Report of a Case, Arch. Neurol. & Psychiat. **41**:580 (March) 1939.

The purposes of the present paper are to report a new case of unilateral lobectomy in a man, in which the poverty of effect is illustrated, to describe a new symptom presented by this patient, which supports interpretations of function of the frontal lobe made previously, and to consider the anatomic deductions just mentioned.

REPORT OF CASE OF RIGHT FRONTAL LOBECTOMY

History.—E. A. Q., a white man aged 40, was referred by Dr. William Chorba on Oct. 20, 1937. On Sept. 14, 1935, March 25, 1936, Sept. 19, 1937 and Oct. 18, 1937 there had been attacks of generalized convulsions, starting with a cry and accompanied by unconsciousness. There had been no localizing signs except that each seizure commenced with turning of the head and eyes to the left. The clonic convulsive movements were succeeded by generalized rigidity. Incontinence did not occur. In three of the seizures the tongue was bitten. The seizures were variable in duration. They were followed by transient torpor and confusion. There was always amnesia for the attacks.

The attack of Sept. 19, 1937 commenced when Q was watching to see if an automobile driver was going to pass a red light and he had to crane his neck to the left. He found himself unable to turn his gaze away from the light, and this fixed position merged into the seizure itself. The last paroxysm also began with fixation of gaze, when, in passing, he glanced at the eyes of a young lady in his office. He could not avert his gaze, and the full seizure began while he was staring at the woman's eyes.

In addition to the major seizures, there were about fifty minor ones, most of them occurring in the period between March 25, 1936 and Sept. 19, 1937, during which interval there were no major incidents. These minor episodes, which lasted perhaps half a minute, consisted of fixation of gaze with rotation of the head to the left and, occasionally, one or two twitches of the muscles of the neck. The patient remained fully conscious during these attacks, and there was no amnesia.

There were no other symptoms whatever, with the exception of one which evidently has not been described before—conscious inability to synthesize recognized thoughts. Particularly, no changes in personality or other mental symptoms were noted. The past and personal history contained no relevant information except that no symptom similar to the present ones had occurred previously.

Symptom of Conscious Inability to Synthesize Recognized Thoughts.—The single additional symptom was of considerable interest from the standpoint of interpretation of function of the frontal lobe. The patient's work was ideally suited to the demonstration of the phenomenon. He was employed in the stock transfer and dividend department of a large corporation, in New York, which is concerned with the transfer of stock from one owner to another, the original owner usually being deceased. On May 15, 1938, six and one-half months after right frontal lobectomy, Q dictated a description of the work in this department. Part of Q's description is given verbatim, in order to show his orderliness of thinking and the preservation of synthesis of complicated material following unilateral lobectomy. Such a clear, complete account would have been impossible for A (the patient with double lobectomy) to make, as is shown in many comparable examples in the detailed description of his case.[1a]

Q described his work in part as follows:

"The transfer has been approved by one of those authorized to approve it. We will assume that the stock was registered in the name of B, deceased, and that F was the duly qualified executor of the estate, who wished to have the stock certificates in question transferred to his individual name. The transfer had been approved by some one in authority at the head office of the corporation, which meant that it was ready for me to work on. In order for a transfer to be made from the name of B to F individually, besides having a court-certified copy of F's appointment as executor, a court-certified copy of B's will and a New York tax affidavit, it is also necessary that we be furnished with an affidavit, preferably by the attorney for the estate, stating that all debts, legacies and administration charges have been duly paid or amply provided for without recourse to the shares that we are requested to transfer. The volume of work is terrific, and there are instances where those who are empowered to approve such transfers may overlook this affidavit regarding the debts."

Q's work consisted of checking over the data which had been approved and ascertaining whether the record was complete and in good order. He had to report errors to his superior, calling attention especially to the absence of any one of the documents which should have been present. Most often the affidavit concerning debts was missing, for adequate reasons which Q explained.

Q had always been extremely capable in the performance of this work. During the period of the minor attacks Q often encountered a certain difficulty in making his report to his superior. It occurred only if he was having a minor attack at the time. He found it impossible to hold all of the facts together in mind, as a unit. For example, he knew that he was dealing with (1) transfer of stock from B to F, (2) a certified copy of F's appointment as executor, (3) a certified copy of B's will, (4) a New York tax affidavit and (5) absence of a required affidavit concerning payment of debts. He knew that the absence of the tax affidavit was the crucial point in his report. He found it impossible, however, to think of all five points together, so that they composed a unit in his mind—a single sequential, coherent entity. The first four components could be brought together properly to form a unitary picture, but the important factor, the missing affidavit, could not be joined with that picture. The idea of the missing affidavit would "recede" from the totality comprised of the other four points, and the harder Q tried to amalgamate it with the other thoughts the farther it would recede. All this time the receding idea would retain its discrete individuality, Q remaining well aware that "the affidavit concerning debts was missing" and of what a debt affidavit was. (An analogy could be made with Q's initials. It was as though he knew that the initials E., A. and Q. were those of his name, and he could think of E. and A. as composing the unit E. A. But although he knew the initial Q. and knew that it belonged after E. A., he could not think of it so as to make the unit E. A. Q.) The experience would transpire while Q's head was forcibly turned, or sometimes twitched, to the left in a minor attack. At other times when he was having a minor seizure he did not note such disturbance or any other mental symptom—perhaps, as he himself stated, because nothing was happening which would serve as material for the symptom.

In the first postoperative week this symptom recurred in all-inclusive form. Q had difficulty in holding any thoughts together at all. During that week the course was uneventful except for fever, in which the temperature rose to between 100 and 101 F. daily. No infection of the wound or of any other part was discovered. During this period Q's behavior was normal except that often, when he was conversing with me, it seemed as though he were looking past

instead of at me and his speech came as though the thoughts behind it were labored. All others who talked with him reported the same experience.

After the first week the temperature became normal, and the peculiarity of expression disappeared. Then, when questioned about it, Q said that speech had indeed been difficult—that it was very hard to hold thoughts together. Thoughts "fell away" from each other, he declared. An assemblage of thoughts was difficult to hold intact—the components tended to separate from one another. This appears again to represent the conscious inability to synthesize thoughts already described. During the first postoperative week the symptom occurred whenever Q conversed; it was not associated with seizures, of which there have been none, minor or major, since the day of the operation. It was only after this experience that Q told of the similar experiences which he had had before operation.

Psychologic Tests.—The results of psychologic tests, both before and after operation, which were performed at the Neurological Institute of New York by Miss Gladys Tallman, will be reported separately by her. The preoperative and postoperative scores are summarized together, for convenience in comparison. The scores follow:

Preoperative Results	Postoperative Results
Oct. 28, 1937. Date of birth: Oct. 22, 1897. Chronologic age: 40 yr., 6 days.	Dec. 27, 1937. (Operation: Oct. 30, 1937)
Stanford-Binet Test	
Score: 20 yr., 8 mo.; intelligence quotient, 1.38. The highest score which he could have attained is 22 yr., and the intelligence quotient, 1.52.	Score: 21 yr., 4 mo.; intelligence quotient, 1.42.
Arthur Test	
Score: 18 yr., 3.5 mo.; intelligence quotient, 1.22.	
Cornell-Coxe Test	
Score: 16 yr., 8 mo	Identical with the preoperative score
Stenquist Test	
Score: above the average norms.	
Kent-Rosanoff Test	
The patient's responses closely followed those expected from the average person.	The responses were surprisingly similar to those given before his operation.
Rorschach Test	
The patient's responses were practically all anatomic. The full report will be presented separately by Dr. Bruno Klopfer.	The patient's reactions at this time showed far less concern with anatomic structures than they did in the first place. According to the test, he showed no difficulty in mental function.

Neurologic Examination.—The following significant findings were made preoperatively, all other tests, including examination of the optic fundus, giving normal results in repeated examinations: the right arm swung less well than the left in walking; the left knee and ankle jerks were slightly more active than the right; the left plantar response was less active than the right; there was questionable smoothing of the right side of the face.

The patient was perfectly oriented in every way and gave the impression of being unusually intelligent. He was well informed about general and personal affairs. There were no evidences of euphoria or unusual facetiousness. No indications of aphasia or apraxia were found.

Roentgen Examination.—A roentgenogram of the skull, made by Dr. Cornelius Dyke, revealed the following: "Involving the superior and middle frontal gyri, about 16 mm. lateral to the midline, there was an irregular, linear streak of

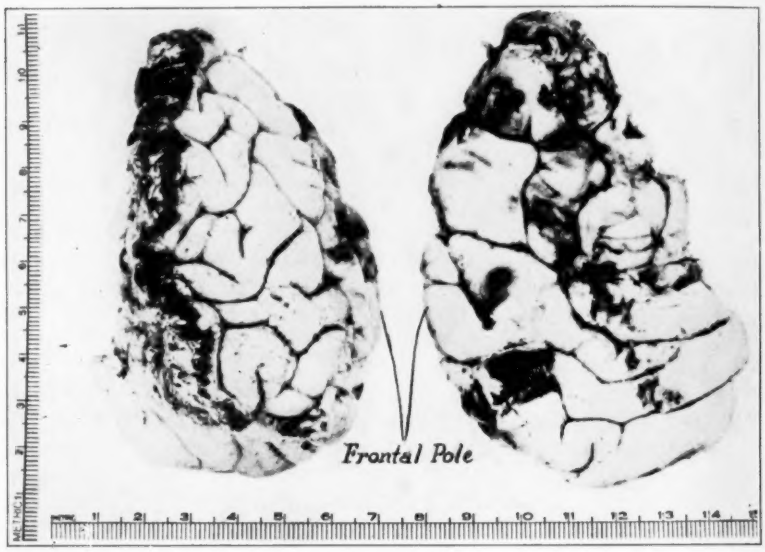

Fig. 1.—Lateral (left) and mesial (right) views of the amputated right frontal lobe.

calcification. At another point, in the main mass, there was a parallel streak. I believe that this calcification involved a glioma, and not a meningioma. The impression was that of a right frontal astrocytoma. No evidences of increased intracranial pressure were found."

Operation.—On Oct. 30, 1937 right frontal lobectomy was performed by Dr. Leo Davidoff, at the Neurological Institute, with the patient under procaine anesthesia. The lobe contained a large astrocytoma, diagnosed as such by Dr. Abner Wolf. The weight and dimensions of the specimen removed (fig. 1) were:

Weight	153 Gm.
Length	9.5 cm.
Longest dorsoventral dimension	7 cm.
Greatest width	5.5 cm.

An abstract of Dr. Davidoff's operative report follows.

Excision of the right frontal lobe was carried out in the following manner: A pacchionian granulation was divided by means of cauterization and silver clips, the attachment between the frontal lobe and the superior longitudinal sinus thus being freed superiorly. The lobe was then gently retracted from the falx cerebri, both the right and the left anterior cerebral artery and the anterior communicating artery being exposed. The right anterior cerebral artery was clipped in two places and divided. The inferior and middle frontal vessels arising from the branches of the anterior cerebral artery in the sylvian fissure were next divided between silk ligatures and silver clips when ligatures could be placed. The lobe was then excised with the electrocautery knife, in a straight line, vessels being clipped or cauterized as they were encountered. The specimen is illustrated in figure 1.

Complete hemostasis was effected. The resulting cavity was filled with warm solution of sodium chloride and the dura closed tightly with interrupted silk sutures.

Shortly after ligation of the right anterior cerebral artery the patient suffered a brief clonic convulsive seizure involving the left side, which was witnessed by the anesthetist. An accurate description of this cannot be obtained, owing to the presence of drapes and other obstructions. There was no recurrence of this episode. The patient did not respond during this seizure, but immediately afterward responded as usual.

The right olfactory nerve was severed with the electrocautery. As this was done the patient experienced a burning sensation in the right nostril, but noted no abnormal olfactory sensation.

The vital signs were satisfactory throughout the operation. Bleeding was negligible. The patient was returned to his room in good condition.

Postoperative Course.—A few weeks after the lobectomy, Q showed no behavioral changes of any variety. During the first week after leaving the hospital he insisted on having sexual intercourse with his wife three times a day. After the first week he demanded it once in twenty-four hours for a period. In the course of time his sexual expression receded to its old frequency of two or three times a week.

In every other way, Q has appeared entirely normal. He states that he has no symptoms of any kind. His wife and employer agree that he is his usual self and that no peculiarity of any kind can be detected (other than the transiently exaggerated sexual drive). He returned to work two months after the operation and, according to his employer, is performing it as well as ever. In giving his reports he tends to be somewhat circumstantial—behavior which sometimes follows injury of the frontal lobe. In Q's case, however, it cannot be attributed to the disturbance of this region, because it has continued unchanged for many years. Of interest is the fact that there is no alteration in it now.

Q's lack of postoperative change is further indicated by the results of the postoperative series of psychologic tests, which have already been tabulated, with the preoperative scores. Especially to be noted in Q's intelligence quotient of 1.42, as measured by the Stanford-Binet test. Before operation it was about the same—1.38.

COMMENT AND INTERPRETATIONS

Synthesis as the Main Intellectual Function of the Frontal Lobe.—A number of observers have expressed the opinion that the frontal lobes act in a synthesizing capacity as far as intellect is concerned. After

study of the case of bilateral frontal lobectomy previously referred to, it was deduced that the intellectual functions of the frontal lobes are probably limited altogether to synthesis. The matter was summarized as follows:[1e]

> The patient's symptoms are numerous. None of them indicates an alteration in the fundamental nature of any mental process, but only the impairment of its completeness. Hence, the changes are fundamentally not qualitative, but quantitative in nature.
>
> Only one function is considered as primarily affected. This is the elaborate association or synthesis into complex structures of the simpler engrammic products associated in the more posterior parts of the brain. There is a diminution in the amount of this synthesis, which places a limit upon the degree of attainable complexity of thought. Through this deficiency, the large variety of secondary and tertiary defects becomes manifest, and the overt personality appears to be greatly altered. [All excepting a small group of symptoms can be explained on the basis of diminution in synthesizing capacity.] . . .
>
> The deduction has been drawn that the frontal lobes are not intellectual centers in any sense except, perhaps, a quantitative one, and that they play no specialized rôle in intellectual function. They add to intellectual intricacy in a quantitative manner only, by increasing the number of possible associations between engrammes which have already been aggregated to a complex degree in other parts of the nervous system.

This focal defect—impairment of intellectual synthesis—was revealed directly, as in A's increasing difficulty in solving algebraic equations as they became progressively complex, although none were beyond the capacity of an ordinary high school graduate. It was also shown less directly by impairment in restraint in the control or concealment of feeling. This was indicated especially in A's exaggerated expression of self-aggrandizing thoughts and in his relatively free vent of chronic, mild hostility toward certain persons, with occasional tantrum-like outbursts. The normal restraint over these and similar processes was reduced in A, and the belief was expressed that this restraint, in itself, results from the action of intellectual products synthesized to a high degree.

Until now, the idea that synthesis is a major intellectual function of the frontal lobes has been the result of deduction. Positive evidence is to be found, presumably, in Q's symptom of conscious inability to synthesize recognized thoughts. Only one probably similar experience has been noted in the literature. A patient of Sterling's[2] who had a glioma invading the entire corpus callosum, as well as both hemispheres, asserted that in the first moments after a question concerning his past had been asked him he seemed to know the object of the question,

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2. Sterling, W.: Ueber die psychischen Störungen bei Hirntumoren, Ztschr. f. d. ges. Neurol. u. Psychiat. **12**:147, 1912.

but that the more he thought about it the more clearly he felt that the "content of the question was escaping him—receding farther and farther from him." Sterling gave no interpretation. The symptom probably will be encountered more frequently if it is sought.

It is of interest to consider the effect on Q of his conscious deficit in synthesis. Q said that it led to confusion and loss of self confidence. Such symptoms as these have often been thought of as primary manifestations of injury of the frontal lobe. It is worth while to note that they are anything but primary and that they, and probably many similar disorders, may be the derivatives of disturbances such as impairment of synthesis. Synthesis is a more fundamental process, in a physiologic sense.

Synthesis of simpler into more complex units means the same in the "neurointellectual" as in the neuromuscular sphere. In the neuromuscular field one is accustomed to think of complexity as the combined, or synthesized, action of more as compared with fewer neuromuscular groups. Such association or synthesis is mediated by such cell groups as the corpus striatum and the premotor area.

The establishment of patterns in the domain of intellect can be thought of as similar. This identity between the "neurointellectual" and the neuromuscular system is one of the links in a structural theory of thinking which is to be presented later. The identity helps in thinking of intellect strictly as a function of neurons and in seeing its manifestations in the image of neuromuscular processes, which are more concrete and less mysterious. The nonmotor part of the frontal cortex amalgamates simpler units of intellect into new and more complex structures, just as the premotor cortex does for neuromuscular combinations. The synthesizing function of the frontal lobes was fully discussed in the earlier report on A,[1a] as were many collateral evidences that synthesis is indeed the major function of these lobes.

Among other examples which support the concept of the synthetic function of the frontal lobes are the slight defects in cases 1 and 2 of Penfield and Evans.[3] In case 1, the patient had difficulty in performing simultaneously enough steps so that all the components of a simple supper would be ready at the same time. In case 2, the patient's incompetence in performing mental arithmetic, although written arithmetic could be done without trouble, appears to illustrate the same thing.

Contrast Between the Consequences of Unilateral and Those of Bilateral Frontal Lobectomy.—The symptoms shown by A after bilateral lobectomy were many and comprehensive when seen as a group, and

3. Penfield, W., and Evans, J. P.: The Frontal Lobe in Man: A Clinical Study of Maximum Removals, Brain **58**:115, 1935.

clinically they involved every phase of his behavior. A's symptoms, as such, were similar to those often described in cases of injury of the frontal lobes of various types. The advantage in his case was that the symptoms were due to removal of tissue, the situation being uncomplicated by pressure, vascular change, toxemia or other extraneous factors. However, because A's symptoms were typical manifestations of injury to the frontal lobes, it was thought that A's case and those of the various sorts of frontal injury described in the literature gave each other mutual support. Hence it was considered that the conclusions derived from A's case could be generalized.

In contrast to the all-embracing changes following bilateral lobectomy or other massive injury, the intellectual and emotional changes following removal of one frontal lobe are strikingly slight and few, as has been agreed by all observers.

Fulton and Jacobsen [4] and Jacobsen [5] expressed the conviction that this is so as the result of experiments on monkeys and chimpanzees, as did Messimy and Finan,[6] from observations on monkeys only. Penfield and Evans [3] and Fox and German [7] in the first studies on patients after unilateral frontal lobectomy, reported the same results. In cases 3 and 4 of Penfield and Evans (in 1 of which right, and in the other left, lobectomy was done, for relief of post-traumatic epilepsy) no postoperative changes in behavior were detected. In case 2 (in which there was left lobectomy for post-traumatic epilepsy) the patient was normal except for diminution in initiative, fatigability, scatter in the performance of the Binet-Simon test and difficulty in doing arithmetic mentally, although he could calculate normally if permitted to write. In case 1 the alterations were the most definite although they were still relatively slight. The right lobe had been removed, because of tumor. After operation the patient found herself "a little slow" and a little

4. Fulton, J. F., and Jacobsen, C. F.: The Functions of the Frontal Lobes: A Comparative Study in Monkeys, Chimpanzees and Man, in Proceedings of the Fifteenth International Physiological Congress, August 9 to 16, 1935, Leningrad, Moscow, State Biological and Medical Press, 1938, p. 113.

5. Jacobsen, C. F.: The Effects of Extirpation of the Frontal Association Areas in Monkeys upon Complex Adaptive Behavior, Am. J. Physiol. **109**:59, 1934; Functions of Frontal Association Area in Primates, Arch. Neurol. & Psychiat. **33**:558 (March) 1935.

6. Messimy, R., and Finan, J.: Les effets, chez le singe, de l'ablation des lobes préfrontaux: Modifications de l'activité et du mode réactionnel, Compt. rend. Soc. de biol. **126**:201, 1937.

7. Fox, J. C., Jr., and German, W. J.: Observations Following Left (Dominant) Temporal Lobectomy: Report of a Case, Arch. Neurol. & Psychiat. **33**: 791 (April) 1935.

"incapable," and she "could not think well enough." An important illustration of her difficulty follows:

> One day about fifteen months after operation she had planned to get a simple supper for one guest and four members of her own family. She looked forward to it with pleasure and had the whole day for preparation. This was a thing she could have done with ease ten years before. When the appointed hour arrived she was in the kitchen, the food was all there, one or two things were on the stove, but the salad was not ready, the meat had not been started and she was distressed and confused by her long-continued effort alone. It seemed evident that she would never be able to get everything ready at once.

The authors expressed the opinion that her defect was "a lack of capacity for planned administration."

In the 2 cases of Fox and German the postoperative changes also were slight. One patient showed only dearth of spontaneous motor responses. The other had moderate euphoria and disturbance of appreciation of spatial relations.

Vincent and Dereux[8] described a man who survived amputation of the anterior two thirds of the left frontal lobe, Broca's area having been left intact. They stated that after operation the patient behaved entirely normally. There was no mental disturbance, "especially of judgment, memory, character or affectivity." Also, there was no euphoria, no tendency to puerility and no disturbance of spatial orientation.

Jefferson[9] reported the largest single series of unilateral frontal lobectomies. He described 8 cases: 5 of right and 3 of left lobectomy, with sparing of Broca's area. All the patients with left lobectomy and 3 of those with right lobectomy were observed over periods sufficiently long for study. Jefferson's conclusions, identical with those of the other authors, were that no important changes occur after unilateral lobectomy and that the right and the left lobe are identical from this standpoint. After a thoughtful consideration of the subject, he stated:

> "Frontal" changes will be most pronounced when the lesion is bilateral (as in callosal tumors) or when it is invasive, or when pressure is high or in combinations of these conditions.

After right hemispherectomy the intellectual and emotional changes are similarly slight. Dandy,[10] reporting the first cases in which the whole right hemisphere was removed in man, detected no change in

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8. Vincent, C., and Dereux, J.: Gliome frontal gauche: Résection du lobe frontal; considérations physiologiques (état mental et épreuve de Delmas-Marsalet), Rev. neurol. **67**:411, 1937.

9. Jefferson, G.: Removal of Right or Left Frontal Lobes in Man, Brit. M. J. **2**:199, 1937.

10. Dandy, W.: Removal of Right Cerebral Hemisphere for Certain Tumors with Hemiplegia: Preliminary Report, J. A. M. A. **90**:823 (March 17) 1928.

intellect and emotion. Three of the 5 patients survived long enough to be observed over considerable periods after operation. Gardner,[11] reporting another case of right unilateral hemispherectomy, found no intellectual or emotional changes except optimism "bordering on euphoria. Gardner's patient was also studied by O'Brien,[12] who wrote:

> In the mental sphere she appeared stabilized, and there was no evidence of emotional instability. She did appear to the casual observer to be slightly apathetic at times, but from her intimate friends I am unable to learn of any evidence of mental deterioration or marked personality change.
>
> . . . Her memory for recent and past events was good, and she read constantly in spite of her eye difficulty [hemianopsia].
>
> . . . She took the usual interest in her children and attended very well to her household duties. She inquired and was anxious to know all the details of her operation, which was explained to her, and she was extremely grateful for what had been done for her.

In McKenzie's[13] case, also, although the patient was of low mental grade prior to the operation, no intellectual or other behavioral changes could be detected afterward.

Anatomic Consideration of the Neurons of Intellect.—The marked deficit in synthesis in cases of bilateral frontal lobectomy or other bilateral injury, on the one hand, as compared with the paucity of such deficit after unilateral lobectomy or hemispherectomy, on the other, supplies pivotal information on the anatomic structures concerned with thinking.

That difference must mean that the component of intellectual function executed by the frontal cortex is bilaterally represented anatomically. Each frontal intellectual combination, or "engram," must be represented in each frontal lobe. The neurons for each caudal engram must connect with frontal neurons on both the right and the left side. This means that the caudofrontal neurons must undergo partial decussation, the fibers undoubtedly passing through the corpus callosum (figs. 2 and 3).

When one lobe is removed no complex idea is lost; in so far as can be demonstrated, the patient thinks as he always did. This is exemplified in figure 4, which shows how when one frontal lobe is absent the connections on the other side still serve adequately.

On the other hand, if both lobes are removed or otherwise injured the more complex combinations can no longer be formed. The simpler ones can still be made, however (fig. 5).

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11. Gardner, W. J.: Removal of the Right Cerebral Hemisphere for Infiltrating Glioma: Report of a Case, J. A. M. A. **101**:823 (Sept. 9) 1933.

12. O'Brien, J. D.: Removal of the Right Cerebral Hemisphere: A Case Report, Ohio State M. J. **28**:645, 1932; Further Report on a Case of Removal of Right Cerebral Hemisphere, J. A. M. A. **107**:657 (Aug. 29) 1936.

13. McKenzie, K.: To be published.

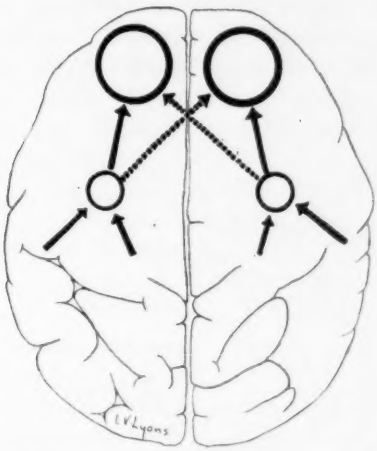

Fig. 2.—The small circles represent relatively simple "caudal" engrams, synthesized from still simpler ones. For the sake of clarity in the drawing, the "still simpler" engrams are indicated merely by the arrows converging on the small circles. The large circles signify the most complex engrams, formed by the synthesis of those represented by the small circles. The partial decussation is indicated only for this particular caudofrontal synthesis, in order to make the diagram simpler and more legible.

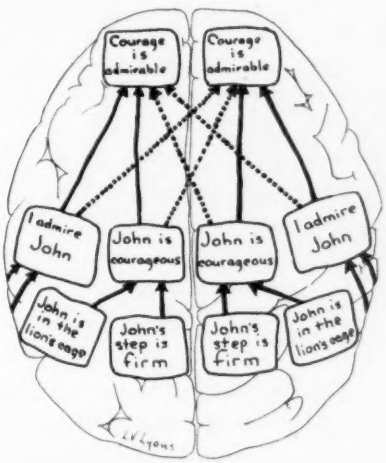

Fig. 3.—Anatomic representation of normal thinking. The meaning is the same as that expressed in figure 2. Instead of circles, actual thoughts are represented. Most caudally the thoughts are simplest. A way is shown in which the complex thought "courage is admirable" may be constructed out of a number of simpler engrams.

The partial decussations should really be indicated throughout, in the whole caudofrontal relationship. This was not done, for the sake of clarity. The principle is shown, however, by the occurrence of each engram on each side.

The division into the caudal and the frontal cortex is, of course, arbitrary. The principle of partial decussation of caudocephalic neurons subserving intellect must occur without interruption, all the way from the occipital pole. This is shown by the cases of hemispherectomy in which there is no more deficit of synthesis than in those of unilateral frontal lobectomy.

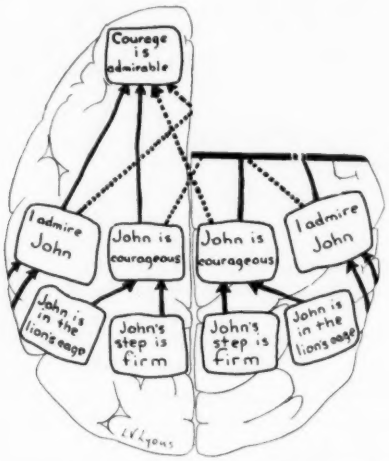

Fig. 4.—Effect of unilateral lobectomy. Complex thinking is preserved after unilateral lobectomy. The complex thought "courage is admirable" may still be constructed.

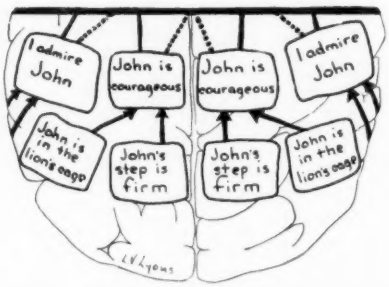

Fig. 5.—Effect of bilateral frontal lobectomy. The complex thought "courage is admirable" can no longer be constructed. The simpler units of thought are not disturbed.

Bilateral representation, with partial decussation of the projection pathways, is well known in the neuromuscular and neurosensory apparatus. In those systems bilateral representation occurs in the brain whenever the peripheral organ is "paired"—that is, whenever the right and the left organ always act as one. Kappers, especially, has stressed and illuminated this matter. Examples in the motor sphere are the fore-

head, tongue, jaw and larynx. The pyramidal fibers supplying the nuclei for the muscles of these parts are both crossed and uncrossed; thus, both the right and the left motor cortex are connected with both the right and the left nucleus (e. g., hypoglossal nucleus). This explains the fact that in cases of hemiplegia caused by a lesion in one internal capsule, the forehead, tongue, jaw and larynx are not paralyzed, but are only weakened if, indeed, they are detectably affected at all. On the other hand, these parts are paralyzed when the pathways on both sides are destroyed, as in pseudobulbar palsy. The bilaterality of pyramidal innervation of these and other organs is well demonstrated in the cases of hemispherectomy cited. In some cases there was weakness of one or another of the paired muscle groups, while in others there was none; in no instance, however, did paralysis occur.

Similarly, bilateral representation occurs in the sensory domain, when the anatomic and functional arrangements are paired, as in the visual, auditory and vestibular systems.

The evidence which suggests bilaterality of representation in the "neurointellectual" system helps to aline that system with the neuromuscular and neurosensory ones. It is difficult to escape the concept of such bilaterality in the "neurointellectual" field as an explanation of all the facts. It is less vague and is easier to define than the idea that the brain "acts as a whole" so that it is the quantity of brain rather than the region which is important. Nor, for that matter, does the latter theory take all the facts into account—those which show the contrast between the effects of unilateral and bilateral procedures. The concept that one frontal lobe "takes over" the function of the other does not differ from the explanation offered. It appears to be the same, but is less concrete and specific. If the intact lobe does "take over" the function of its extirpated mate it can do so only through a mechanism similar to the one that has been outlined.

SUMMARY

1. A new case of unilateral (right) frontal lobectomy (that of E. A. Q.) is reported.

2. A new symptom of injury to the frontal lobe presented by E. A. Q. is described. The symptom is of conscious inability to synthesize recognized, separate thoughts.

3. The theory of the synthetic role of the frontal lobes in intellectual function is discussed, as is the support given that theory by the new symptom.

4. The slight effects of unilateral frontal lobectomy are contrasted with the panoramic ones following bilateral lobectomy or other bilateral injury. In the light of this comparison, it appears that the caudofrontal pathways of intellect undergo partial decussation.

OCCURRENCE AND DISTRIBUTION OF CALCIFIED PLAQUES IN THE SPINAL ARACHNOID IN MAN

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In 1920 Weed [1] reported on the occurrence in animals of calcified plaques and of the islands of arachnoidal tissue in which they form. He came to the conclusion that the plaques, within islands of arachnoid cells arranged in concentric whorls, are a phenomenon of advancing age. The process of calcification he concluded to be a degenerative one within the whorls, similar to the deposition of calcium elsewhere as a result of degeneration. There is little doubt that the plaques are formed as deposits of calcium in the islands of arachnoid cells (fig. 1). Observations by Weed [1] and by Cushing and Weed [2] have demonstrated this fact satisfactorily.

This report concerns itself with the incidence, sites of occurrence and possible significance of calcified arachnoidal plaques in the spinal arachnoid of man. The material was obtained from 25 consecutive routine autopsies at the Mallory Institute of the Boston City Hospital.

Microscopic sections were from material fixed in solution of formaldehyde, decalcified with a solution of 5 per cent nitric acid in 80 per cent alcohol and stained both by Masson's technic and with hematoxylin and eosin.

Of the 25 specimens 19 presented calcified plaques grossly observed on one or both surfaces of the cord. These ranged from 1 mm. in diameter to 5 by 30 mm. Six of the 25 specimens had no grossly discernible calcified plaque even when examined with a hand lens of a magnifying power of about 4 diameters.

Figure 2 shows the sites of occurrence of plaques on the dorsal and ventral surfaces of the cord.

From the Department of Neurology, the Harvard Medical School, and the Neurological Unit of the Boston City Hospital.

1. Weed, L. H.: The Cells of the Arachnoid, Bull. Johns Hopkins Hosp. **31**:343, 1920.

2. Cushing, H., and Weed, L. H.: Studies on the Cerebro-Spinal Fluid and Its Pathways: IX. Calcareous and Caseous Deposits in the Arachnoidea, Bull. Johns Hopkins Hosp. **26**:367, 1915.

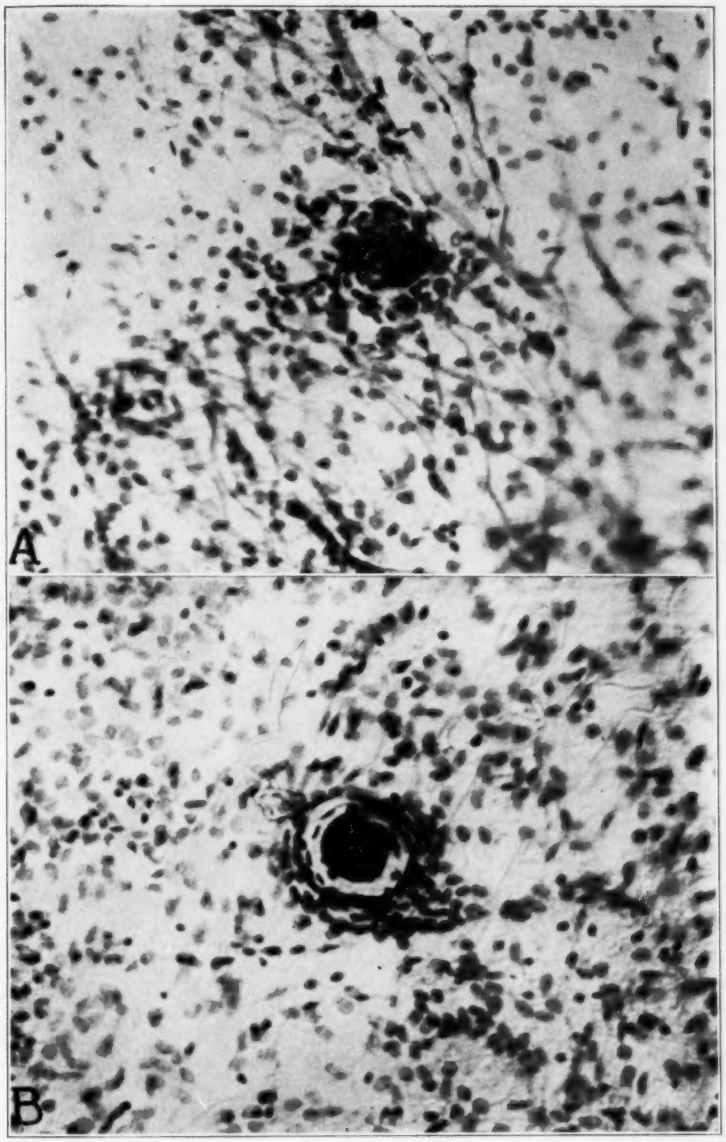

Fig. 1.—*A*, an aggregate of normal arachnoid cells arranged in whorls. The strands that appear in the photograph are arachnoid trabeculae. Methylene blue stain. *B*, the same structure as *A*, with early calcification in its center. Methylene blue stain.

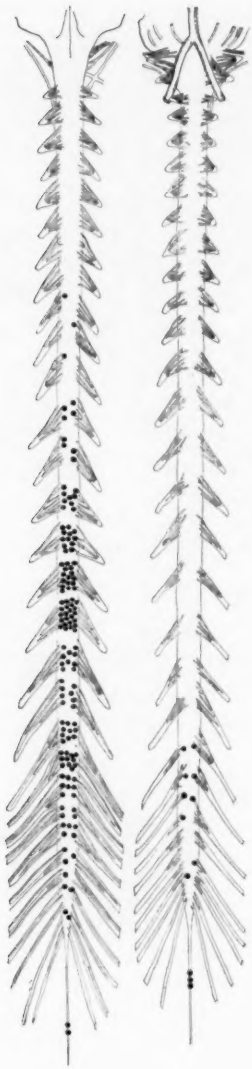

Fig. 2.—Incidence of calcified plaques at the various levels on the dorsal and the ventral surface of the cord.

The predilection for the dorsal over the ventral surface of the cord was, in this series, exactly 11 to 1. This is in accord with Weed's [1] findings. Figure 2 shows that the site of greatest predilection was the thoracic part of the cord, next the lumbosacral and caudal segments and last, with no plaques, the cervical segments. When taken as a unit the lumbosacral and caudal segments are as long as the thoracic, yet the total incidence in the thoracic region of the cord was greater than the

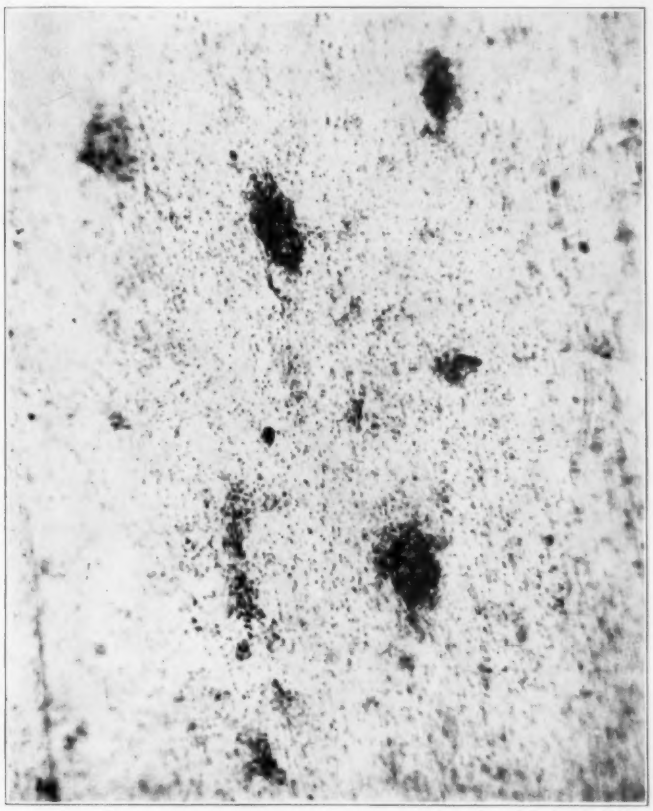

Fig. 3.—Sheet of arachnoid tissue from the dorsal surface of the thoracic segment of the cord. In this particular low power field there are six whorls of arachnoid cells, none of which are calcified. Methylene blue stain.

sum of the total incidence in the lumbar, the sacral and the caudal segment. Therefore, the site of greatest occurrence must be one of selection and not one of chance distribution.

The incidence of calcified plaques in females was 9, while in males it was 10; obviously sex is no factor. The average age at death of patients with plaques was 55.3 years. The average age of those without plaques was 64.1 years. At the Mallory Institute in 1934 the average age of

patients coming to autopsy (infants and the stillborn being excluded) was 53.9 years.

There does not seem to be a common denominator in the systemic diseases or the cause of death for either the group with or that without

Fig. 4.—Large calcified arachnoid plaque, showing the horny nature, the relation to the spinal cord and to the nerve root, the "whorling" structure and the lacunas (which contain arachnoid cells) within the calcification. Masson's stain.

calcified plaques. There was a generalized vascular deposition of calcium in 26 per cent of the cadavers with calcification of the arachnoid and in 33 per cent of those without such calcification.

The argument advanced by Weed,[1] that the calcification of islands of arachnoid cells is in accordance with the advancement of age, is not borne out by this study, particularly since a comparison of the average ages of the two groups showed that patients without plaques were 8.8 years older on the average at death. It is to be emphasized, in addition, that among the patients with calcified arachnoid plaques there was a significant number of young persons, including a boy 12 years old.

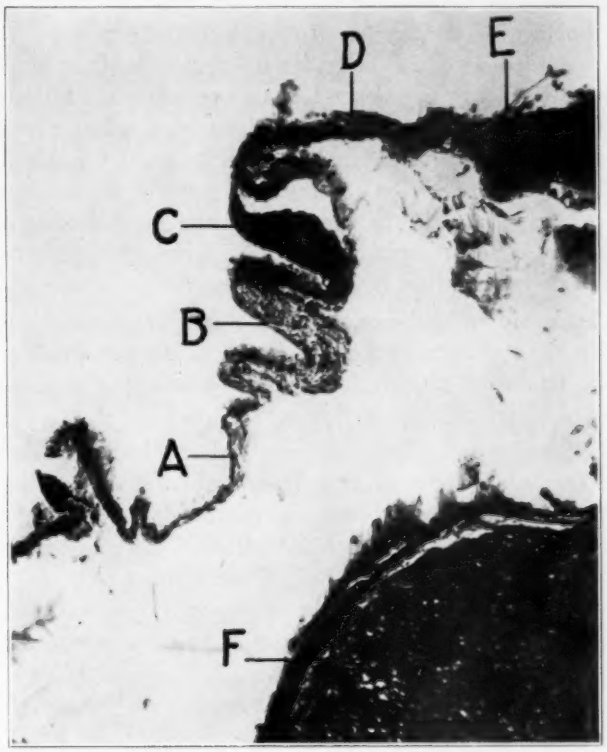

Fig. 5.—Probable method of growth of calcified plaques. *A*, normal arachnoid; *B*, arachnoid whorl; *C*, calcified arachnoid whorl; *D*, normal arachnoid; *E*, calcified plaque; *F*, nerve root.

In an effort to understand the selective occurrence of plaques, sheets of arachnoid tissue from the dorsal surface of the lumbar, thoracic and cervical regions were quickly stained in methylene blue and examined under the microscope. The number of aggregations of arachnoid cells (fig. 3), in which calcium later appears as plaques, per low power field was noted in the three regions, and averages were determined for the examination of several fields. In a like fashion, the number of arach-

noid whorls on the ventral surface was compared with that on the dorsal surface for the same level of the cord. It was found that the greatest number of aggregations of cells, more than twice as many as at any other level, occurred in the thoracic segment. Surprisingly enough, the number in the cervical segment was exactly the same as that in the lumbosacral region. As would be expected, the dorsal surface of the arachnoid at the same level showed about five times as many aggregations as the ventral surface. Weed [1] has made the observation, corroborated here, that the clusters of arachnoid cells are frequently at the point of juncture of the arachnoid sheet and the arachnoid trabeculae. This fact, coupled with the fact that the dorsal surface of the arachnoid is more redundant and hence bears more arachnoid trabeculae, may explain the preponderance of aggregations of arachnoid cells in the dorsal portion. No ready explanation presents itself for the preponderance in the thoracic region or for the fact that despite the equal occurrence of cell aggregates in the cervical and the lumbosacral part of the arachnoid there is never gross calcification in the cervical region (microscopic areas of calcification do frequently occur, however).

It has been said [3] that these calcified plaques give rise to no pathologic process. In the specimens examined in the present study this has been found to be true even though from their appearance the plaques might be thought to be irritating (fig. 4).

Microscopically the calcium is arranged in sheets and whorls and the whole enclosed between two layers of normal arachnoid cells. Adjacent to the plaques are occasional precalcified whorls, and it is by the aggregation of these whorls when calcified that the plaques appear to grow (fig. 5). Within the calcified areas are arachnoid cells contained within lacunas which give the appearance of true osseous tissue. However, the calcium is deposition calcium and not osteogenic calcium.

SUMMARY

The occurrence of deposition calcium in the whorls of cells in the spinal arachnoid of man and their method of growth are noted. This calcification does not occur in a chance arrangement but shows a predilection for the thoracic segments and a further predilection for the dorsal over the ventral surface of these levels. A ready explanation for these phenomena is not at hand. Age or general systemic deposition of calcium does not correlate well with calcification in the arachnoid whorls. In the material studied no pathologic significance was observed, although the calcified plaques were angular and horny.

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PINEALOMAS

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Tumors of the pineal body, because of their diversity in histologic structure and clinical manifestations and the difficulty of their operative removal, constitute an interesting and challenging group of neoplasms. Although the clinical picture of these tumors has been rather well established, the same cannot be said for their histogenesis. Haldeman,[1] who reviewed the literature in 1927, found 113 cases that had been reported since 1800. The variety of names used to designate these neoplasms is astounding. In the cases that he collected the tumors were designated as fibromas, psammomas, psammosarcomas, sarcomas, gliomas, gliosarcomas, carcinomas, neuroepitheliogliomas, adenomas, adenocarcinomas, neurogliomas and pinealomas.

In the face of such confusion, the works of Marburg,[2] Krabbe[3] and Tilney and Warren[4] and, more recently, the studies of del Río Hortega,[5] Berblinger,[6] Horrax and Bailey[7] and Globus and Silbert[8]

From the Section on Pathologic Anatomy (Dr. Baggenstoss) and the Section on Neurologic Surgery (Dr. Love), the Mayo Clinic.

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have done much to elucidate the histogenesis of the pineal body and its neoplasms. There is much, however, that is controversial in the accumulated data. The occurrence of neuroglia cells in the normal pineal body and the belief that gliomas may arise from them are disputed points. Horrax and Bailey, Berblinger and others have described spongioblastic pinealoma, while Globus and Silbert refused to recognize such an entity. The question of the relation of the syndrome macrogenitosomia praecox to tumors of the pineal body is also unsolved. Because of these and other differences of opinion, there is as yet no unified conception of these tumors, and, as Berblinger has said, investigators must continue to collect and critically to report data until sufficient evidence has accumulated to warrant accurate conclusions.

The purpose of this paper is to report a study of 10 cases of tumors of the pineal body which have been observed at the Mayo Clinic in twenty-three years. In all these cases the diagnosis was verified by microscopic examination. Four of the cases, because of their unusual interest, will be described in detail. Consideration of the clinical and pathologic features, however, will be based on data derived from all the 10 cases. Necropsy was carried out in the 8 cases in which the termination was fatal.

HISTOLOGIC PROCEDURES

In the cases in which operative procedures were carried out, fresh frozen sections were stained with Terry's modification of Unna's polychrome methylene blue solution. This method facilitates the study of nuclear and nucleolar detail and is of considerable help, as it clearly reveals cytologic evidences of malignancy. The remaining tissue was fixed in a dilute solution of formaldehyde U. S. P. (1:10) and in Zenker's solution. After fixation, frozen sections were stained by MacCarty's method and by Río Hortega's method for staining pineal parenchyma; the paraffin sections were stained with hematoxylin and eosin, with Mallory's differential stain (phosphotungstic acid hematoxylin), with Mallory's modification of Heidenhain's hematoxylin stain, with mucicarmine and with Best's carmine stain for glycogen.

REPORT OF CASES

Case 1.—A man aged 48, who came to the clinic on Aug. 12, 1935, had suffered from severe frontal headache since July 1. He had had photophobia since August 5 and tinnitus and visual hallucinations for three days. On August 10 he noticed transitory weakness of his left arm and hand and felt faint.

Examination of the left side of the body disclosed that Babinski's reflex and Oppenheim's sign were slightly positive and that Chaddock's sign was moderately positive. Visual acuity was 6/12 in the left eye and 6/6 in the right eye. Examination of the ocular fundi disclosed hemorrhages and bilateral choked disks. Otologic examination revealed bilateral nerve deafness.

Ventriculographic examination, which was performed on August 16, revealed bilateral internal hydrocephalus and dilatation of the third ventricle. The ventriculographic findings indicated that the lesion was situated below the tentorium. This procedure was followed by suboccipital craniotomy, but it was impossible to remove the tumor by this approach. The patient's convalescence was normal for

four days after the operation. On the night of the fourth day his temperature increased, and he became restless and irrational. In spite of ventricular drainage the disorientation increased, and severe opisthotonos developed. The condition of the patient became progressively worse, and he died on August 28.

Necropsy disclosed a large hemorrhagic tumor, which measured 4 by 3 by 3 cm. and was situated in the region of the pineal body (fig. 1 *A*). The tumor had

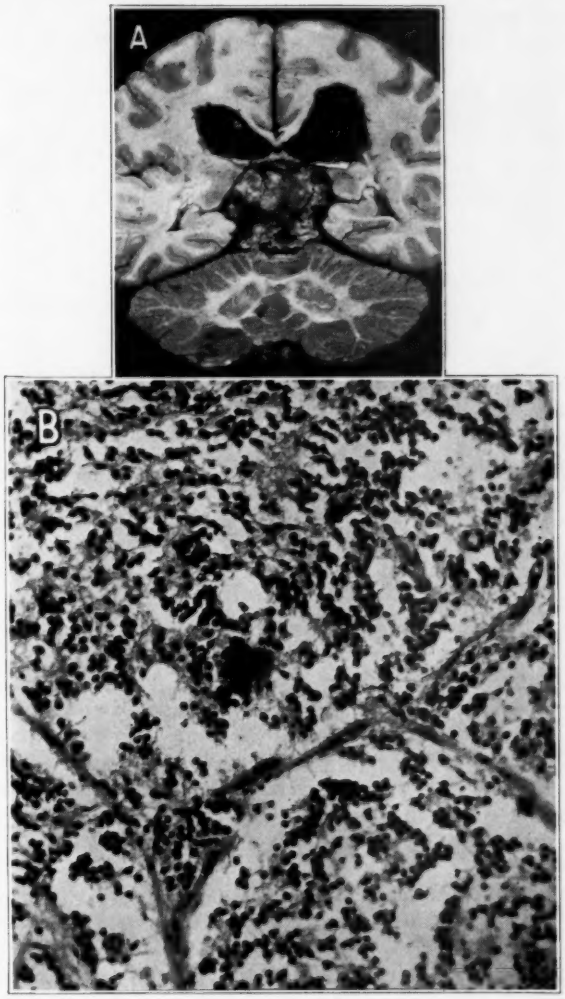

Fig. 1 (case 1).—*A*, compression of adjacent structures by a spongioblastic pinealoma. *B*, section of the tumor; hematoxylin and eosin stain, × 175.

compressed the corpora quadrigemina, the corpus callosum, the crura of the fornix and the thalami, but it had not invaded any of these structures. It extended forward almost to the foramens of Monro and had caused complete obstruction of the third ventricle. There was extensive internal hydrocephalus.

The microscopic appearance was that of a spongioblastic pinealoma (fig. 1 *B*). Staining with hematoxylin and eosin disclosed a preponderance of deeply stained spongioblasts. Mallory's differential stain (phosphotungstic acid hematoxylin) disclosed that some of these cells had fine fibrillary processes. There was a scarcity of large, pale-staining parenchymal cells. In some regions there was noticeable pleomorphism. Large hyperchromatic nuclei, giant cells and mitotic figures were numerous. No trace of normal pineal tissue could be seen.

In this case there was evidence of increased intracranial pressure, but localizing signs were absent. The ventriculographic findings suggested the presence of a subtentorial lesion.

CASE 2.—A man aged 22, who came to the clinic on Nov. 15, 1935, had been well and had worked until December 1934, when he had a "dizzy spell" and fainted. After this attack he had had a dull, constant pain in both eyes. The pain was more severe on the right side and was associated with failing vision. In February 1935 he had begun to have morning headaches in the frontal region and to vomit occasionally. He gradually had become weaker. The frequency of the vomiting and headaches had increased since April 1935. Hiccuping had become frequent. He occasionally had visual hallucinations, but he was not certain whether they occurred on the right or the left side.

When the patient was first examined at the clinic he was pale, thin and weak, and his movements were slow. There was astereognosis of the left hand, and joint sensation was decreased in the left arm and left leg. There was weakness of all the muscles supplied by the left facial nerve. Examination of the right side of the body revealed an increased patellar and a positive Babinski reflex. Perimetry disclosed a left homonymous defect. Visual acuity was 2/30 in the right eye and 2/25 in the left eye. The pupil of the right eye was larger than that of the left. Examination of the ocular fundi revealed extreme pallor of the right optic disk and slight pallor of the left. In each eye the pallor of the optic disk was greater on the temporal than on the nasal side.

The tentative diagnosis was an indeterminate intracranial lesion. Encephalographic examination, which was performed on Nov. 19, 1935, disclosed extensive internal hydrocephalus that involved the lateral and third ventricles. Stereoscopic examination of the encephalograms disclosed calcification situated mesial to the left lateral ventricle, in the region of the aqueduct of Sylvius and a little lower than the normal position of the pineal body. It was thought that the calcification might be situated within a tumor of the pineal body, but it was fully appreciated that such a tumor could not produce all of the symptoms and clinical findings in this case.

The patient did not respond well to the encephalographic study; ventriculostomy was performed in the evening of the day on which the encephalograms were taken. After the ventriculostomy a blood transfusion was administered. The patient's condition improved somewhat, but because of his general condition and the situation of the lesion it was thought that operative intervention was not justified.

The patient returned to his home on November 23. His condition gradually became worse, and he died, at home, on Jan. 22, 1936. The last months of his illness were characterized by the gradual development of blindness, paralysis of the muscles of the left eye, polydipsia and polyuria.

Necropsy disclosed a firm tumor, which measured 4.5 by 4 by 2 cm. and was situated in the region of the pineal body. The tumor filled the third ventricle

completely and extended forward as far as the foramens of Monro. It had caused distention of the third ventricle, had exerted pressure on the cerebellum, midbrain and thalami and had partially occluded the aqueduct of Sylvius. The tumor had become implanted in all parts of the ventricles and on the roots of most of the cranial nerves (fig. 2 *A* and *B*). The posterior lobe of the pituitary body had been almost completely destroyed by a metastatic tumor. There was no trace of a normal pineal body.

Histologically, the tumor consisted of solid nests of large parenchymal cells that were separated incompletely by clumps and columns of small round cells

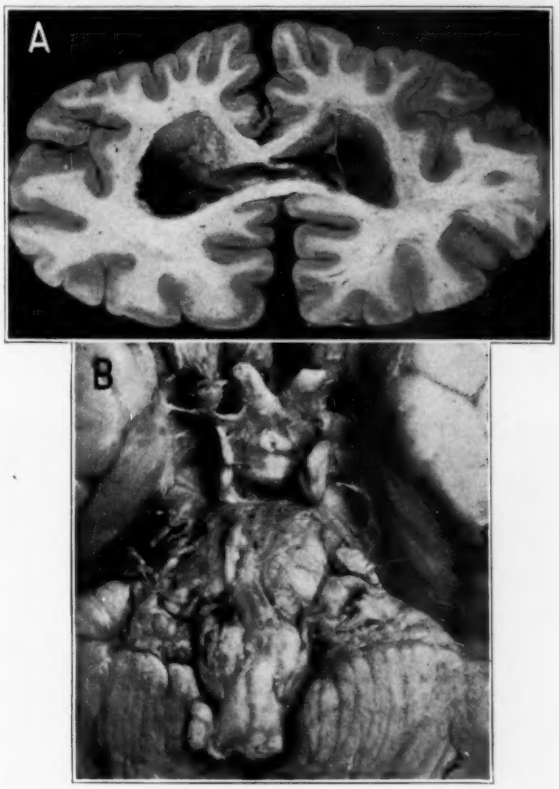

Fig. 2 (case 2).—Implants of pinealoma (*A*) on the walls of the lateral ventricles and (*B*) on the cranial nerves and the base of the brain.

resembling lymphocytes (fig. 3 *A*). It had the mosaic structure of the pineal body of an infant about 2 months of age, but the parenchymal cells were larger than those in the pineal body of an infant of this age. These cells contained large nuclei and immense nucleoli, which stained violet. Mitotic figures, giant nuclei and syncytial, multinucleated masses of cytoplasm were numerous. Occasionally the cytoplasm contained chromatin-like masses that could be considered as evidence of "nuclear excretion." The cytoplasm of these cells was, as a rule, acidophilic and finely granular. Vacuoles or deeply staining hyaline masses were noted occasionally. Between the nests of parenchymal cells were numerous blood vessels and columns

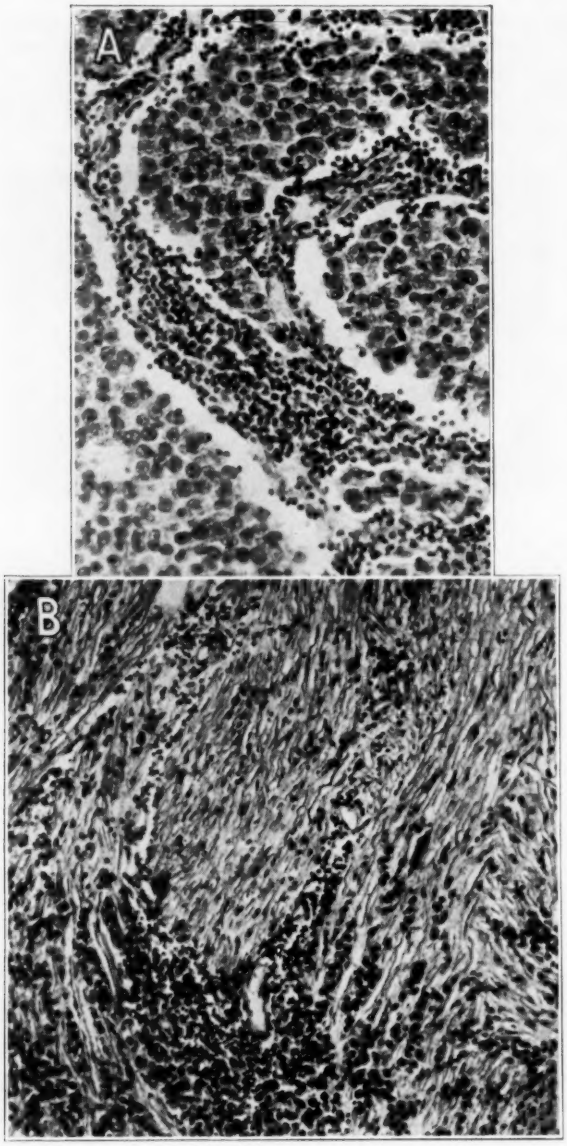

Fig. 3 (case 2).—*A*, characteristic architecture of a pinealoma; hematoxylin and eosin stain, × 175. *B*, implant involving the oculomotor nerve; hematoxylin and eosin stain, × 90.

of small round cells and fibroblasts with fibrillar processes. The small round cells were those that Globus and Silbert called connective tissue elements. Their appearance suggests a mesodermal origin. The metastatic nodules observed in the ventricles and those on the roots of the cranial nerves were identical histologically; they had a tendency to invade the underlying tissue (fig. 3 *B*).

In this case the tumor was a pinealoma that resembled the infantile pineal body histologically. There was extensive invasion of the brain, and implants were seen on most of the cranial nerves. There were signs of a tumor in the contiguous area, and internal hydrocephalus was present.

CASE 3.—A youth aged 18 came to the clinic on March 10, 1937 because of headaches and failing vision. Both these symptoms had been present for ten months. His mother had noticed that he had been drowsy, had lacked energy and had been somewhat irritable for three years before he came to the clinic. Thirst had increased, and the output of urine also had been greater. The headaches first had occurred in May 1936. They were situated over the forehead and in the back of the head; they commenced in the morning and lasted all day. Vision had been poor since May 1936, and glasses were fitted. A month and a half before the patient came to the clinic he had diplopia, which continued for two weeks. In June 1936 he had vomited on two occasions. The vomiting occurred during attacks of headache; it was not projectile. Since August 1936 "spells of dizziness" had occurred about once a day. In February 1937 the portion of the left leg below the knee had become weak during an attack of headache, but the weakness had lasted only five minutes.

Examination at the clinic revealed that the patient was small for his age. He had the appearance of a boy of 12 years; he did not have any beard or pubic hair. Visual acuity was 4/60 in the right eye and 1/60 in the left eye. Papilledema of 2 D. was present in both eyes. Perimetry revealed bitemporal hemianopia and a relative central scotoma. Roentgenographic examination of the head disclosed signs of increased intracranial pressure and secondary destruction of the floor of the sella turcica, the posterior clinoid processes and the dorsum sellae. Small flecks of calcium were visible in the midline, at a level corresponding with the junction of the aqueduct of Sylvius and the third ventricle. These were considered to indicate the presence of an unusually large pineal body or a tumor. It was thought that the patient had the Lorain-Lévi type of pituitary insufficiency. The tentative diagnosis was a tumor of the hypophysial duct.

A right transfrontal craniotomy was performed in order to reach the optic chiasm by an extradural approach. A cystic mass was observed posterior to the optic chiasm, and part of the tumor was removed. Examination of fresh frozen sections revealed that the tumor was a pinealoma. Convalescence was uneventful, and the patient was dismissed from the hospital on March 25, 1937, nine days after the operation. One course of high voltage roentgen therapy was given. Examination on March 29 revealed secondary atrophy of the optic nerves and residual edema of the optic disks.

The patient returned to the clinic for examination on June 10, 1937. He had grown ½ inch (1.25 cm.), and the headaches no longer occurred. Examination revealed some improvement in visual acuity, and perimetry disclosed improvement in the visual fields.

When he again returned to the clinic, on Dec. 8, 1937, he said that his condition had continued to improve. He no longer had headaches or drowsiness, and he had grown 2½ inches (6.25 cm.). Examination of his eyes did not reveal any further change.

He again returned to the clinic on May 14, 1938. In January 1938 dull aching pains had begun to occur in the left calf. In April, after he had undergone a chiropractic treatment, he had had a steady pain in the lumbosacral region. The pain had extended downward into both thighs. As a result of the pain it had been difficult for him to sit or lie down. Examination revealed weakness of the right leg and diminution of the patellar reflex on the right side. The normal lumbar curve of the spinal column had been obliterated. Examination of the eyes again failed to disclose any further change.

Operation was performed on May 21, 1938. Before the operation, a lumbar puncture that was made at the interspace between the twelfth thoracic and the first lumbar vertebra revealed a free flow of cerebrospinal fluid, but when the

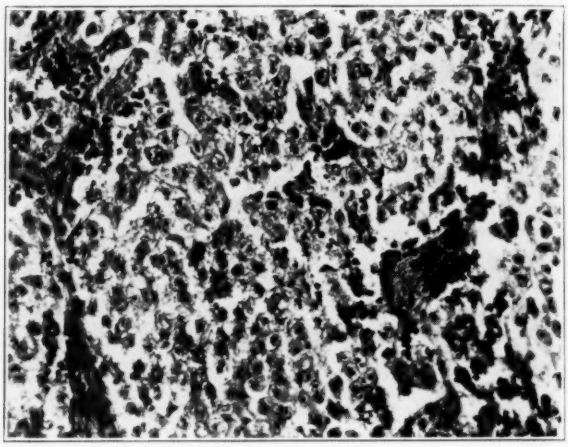

Fig. 4 (case 3).—Extramedullary metastatic tumor of the spinal cord; hematoxylin and eosin stain, × 205.

puncture was repeated at the interspace between the second and the third lumbar vertebra it disclosed spinal subarachnoid block. Laminectomy revealed multiple intramedullary and extramedullary tumors. Some of the tumors were discrete. Two were removed for histologic examination, which revealed that the appearance of the tumors was the same as that of the original pinealoma. No attempt was made to remove all the tumors, as this would have necessitated resection of most of the cauda equina.

Sciatic pain did not occur after the operation. Convalescence was uneventful, except that the patient was unable to micturate. Nine days after the operation, a neurologic examination disclosed increased weakness in the muscles of the anterior part of both legs. Sensation was still intact. When the patient was dismissed from the hospital, on the eleventh day after the operation, he was still unable to micturate, and a retention catheter was necessary.

Histologically, the structure of the tumor resembled to some extent the structure of the pineal body of an infant aged 9 months (fig. 4). The parenchymal cells were

not stained as deeply as those in the tumor in case 2. Mitotic figures were numerous. Examination of the interstitial tissue revealed diminution in the number of cells which resembled lymphocytes and an increase in the number of connective tissue fibers. The transition between the lymphocyte-like cells and the fibroblasts, which has been described by Globus and Silbert, could be observed. The most striking histologic features, however, were the extensive endothelial proliferation in the intima of the blood vessels and the frequency of large, multinucleated giant cells both in the stroma and in association with small blood vessels and capillaries.

In this case an infantile type of pinealoma was associated with symptoms of hypopituitarism. Following partial removal of the tumor from the region of the optic chiasm there was metastatic involvement of the cauda equina.

Case 4.—A man aged 33 came to the clinic on Oct. 6, 1931 because of frontal headache and vomiting, which had been present for two months. The headache had occurred every three or four days and had been relieved by sedatives or vomiting. The vomiting was associated with nausea; it was not related to the ingestion of food and was not projectile. In September the patient had noticed vertigo, blurred vision and diplopia, and there also had been a momentary period of unconsciousness. Some time later he had noticed slight twitching of his right arm and a tendency to fall backward. He had been somewhat confused during the attacks of severe headache. Incontinence of urine and feces had been present for a short time.

The patient had an ataxic gait and right hemiparesis. Examination also revealed paralysis of the facial muscles on the left side and deviation of the tongue to the left. Romberg's sign was positive. Ocular examination revealed immobile pupils and paralysis of the superior recti muscles. Examination of the ocular fundi revealed bilateral papilledema of 3 D., hemorrhages and exudates. Roentgenologic examination of the head disclosed calcification of the pineal body and evidence of increased intracranial pressure. The tentative diagnosis was an intracranial lesion; the dorsum of the midbrain and the posterior part of the third ventricle were considered as possible sites of the lesion. On October 12 ventriculographic examination disclosed extensive internal hydrocephalus and enlargement of the third ventricle. Operation, performed on the following day, included bilateral suboccipital cerebellar craniotomy and decompression. The aqueduct of Sylvius seemed patent; there was no evidence of a tumor of the fourth ventricle, but the arachnoid was thickened and opaque. During the first four days after the operation the patient's condition was satisfactory, but he still complained of severe headache. Frequent drainage of cerebrospinal fluid and intravenous administration of hypertonic solutions were without avail. His temperature increased to 103 F., and he became comatose. He died on Oct. 20, 1931.

Necropsy disclosed a large tumor, which measured 4.5 by 3 by 2.5 cm. and was situated in the region of the pineal body (fig. 5 *A*). The tumor filled the third ventricle and extended forward as far as the foramens of Monro. It had produced distention of the third ventricle. It had compressed the right thalamus and midbrain and had caused necrosis of part of the latter structure. The anterior part of the aqueduct of Sylvius was occluded, and the lateral ventricles were greatly dilated. There also was chronic basilar arachnoiditis.

Histologic examination of the tumor revealed the presence of numerous irregular acini that were lined with tall columnar and cuboidal cells. In some places these cells were arranged in several layers (fig. 5 *B*). The mucicarmine stain

demonstrated the presence of mucus within and without the cells. There also were irregular groups of pineal parenchymal cells that contained large nuclei and nucleoli and numerous mitotic figures. As many as seven mitotic figures were seen in one microscopic field with the high power objective. It was possible to observe various stages of transition between the groups of typical neoplastic pineal parenchymal cells and the mucus-producing, glandlike structures (fig. 6). Cilia could be demonstrated, and many of the acini had definite basement membranes.

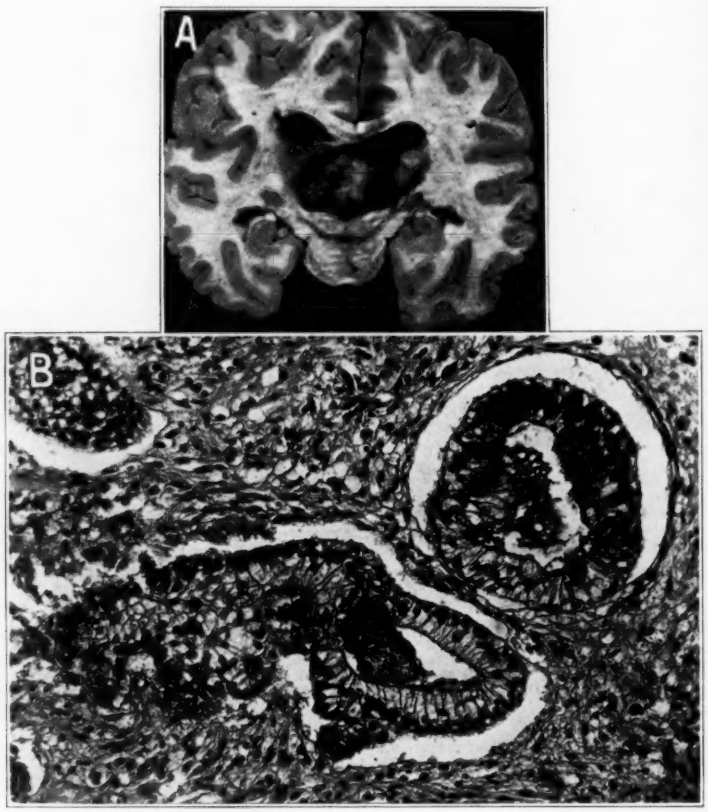

Fig. 5 (case 4).—*A*, compression of adjacent structures by a pineal ependymoma. *B*, section of the tumor showing structure of the tumor and the presence of mucin; mucicarmine stain, × 45.

The interstitial tissue had the appearance of young fibrous tissue; in some regions it appeared almost myxomatous. Special stains were of no help in the identification of this stroma. No trace of normal pineal tissue could be seen.

In this case a pinealoma was associated with signs of increased intracranial pressure, and the ventriculograms suggested the presence of a subtentorial lesion.

NEUROLOGIC SYMPTOMS

Because of the situation of the pineal body and the fact that the symptoms produced by a pinealoma are for the most part the result of internal hydrocephalus secondary to obstruction of the aqueduct of Sylvius, the diagnosis and localization of a tumor of this type are difficult. The symptoms and signs are those usually enumerated as cardinal for a tumor of the brain, namely headache, vomiting and choked disks. In the absence of localizing signs, such as hemiplegia, hemianopia or paralysis of the superior rectus muscle (the last of which is indicative of involvement of the quadrigeminal bodies), the clinical picture is atypical and sometimes confusing. The lesion is usually assumed to be situated in the midline because of the ventricular obstruction and

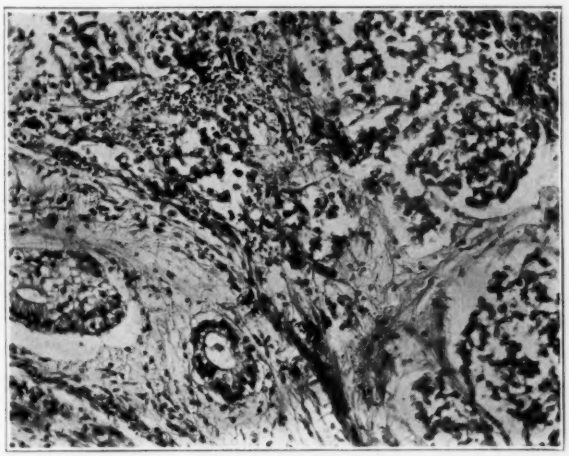

Fig. 6 (case 4).—Transition between well formed acini and groups of cells without acinar arrangement in the tumor; hematoxylin and eosin stain, × 80.

internal hydrocephalus. Since most pinealomas are found in children and young adults and since most tumors of the brain that occur during childhood are in the posterior cranial fossa, pinealomas are most often confused with tumors of the cerebellum or fourth ventricle or with occlusion of the aqueduct of Sylvius either by a tumor or by an inflammatory process. All of these lesions give rise to internal hydrocephalus, and they cannot be differentiated by estimation of the amount of fluid in the ventricles or by the injection of indigo carmine into one lateral ventricle and its recovery from the other. Most of these lesions must be localized by ventriculographic studies. A careful study of the outline of the enlarged third ventricle is often necessary to detect deformities of its posterior end by the projection of a pinealoma into its lumen (fig. 7). In the 8 cases in which the ventricular system

could be examined roentgenologically after the injection of air there was a deformity of the posterior end of the dilated third ventricle. In some cases the deformity was slight, and in several it was not appreciated until all the roentgenograms were collected and carefully reviewed.

In 2 cases ventriculographic studies were not made. In 1 of these (case 3) the findings were those of a lesion about the optic chiasm, and a transfrontal approach to a suspected suprasellar cyst was employed. In another case (not reported) a large calcified shadow in the original roentgenogram of the head led to a preoperative diagnosis of pinealoma.

In the present series of cases the average interval between the onset of symptoms and the patient's appearance at the clinic was eight and two-tenths months. The longest period during which symptoms had

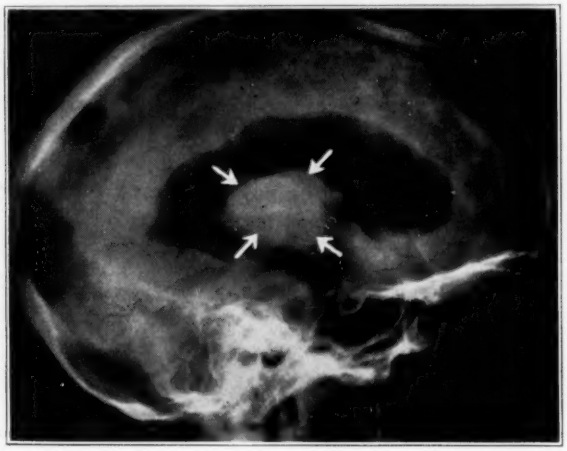

Fig. 7.—Lateral roentgenogram (ventriculogram) showing a large defect in the posterior portion of the third ventricle caused by a pinealoma; the normal sella turcica is unusual.

been present was two and a half years, and the shortest was one month. It is interesting that in 4 cases the symptoms had been present only for two months or less.

Headache was a prominent symptom in all but 1 case. In 6 cases it was the first symptom. In the other cases diplopia, irritability or dizziness was the first symptom.

The objective neurologic findings were based chiefly on disturbances of the oculomotor apparatus, the pyramidal tracts and the cerebellum or its tracts. Paralyses of the ocular muscles occurred in 7 cases. In 3 of these cases there was loss of conjugate movement of the eyeball above the horizontal plane. In 1 case the pupils were fixed, and in 3 cases they failed to react to light.

A positive Babinski reflex was elicited on the left side in 3 cases, on the right side in 1 case and on both sides in 1 case. In 3 cases there was weakness of the muscles supplied by the left facial nerve, and in 2 cases there was weakness of the left arm and leg.

Symptoms and signs indicating involvement of the cerebellum were prominent in 5 cases. Three patients had an ataxic gait; astereognosis was noted in 1 case, and spasticity occurred in another case. In 3 cases there was a tendency for the patients to fall backward.

Choked disks occurred in 8 cases, and in 5 cases the roentgenograms revealed calcification in the region of the pineal body, which suggested enlargement of this structure.

Evidence of an endocrine disturbance was present in only 2 instances (cases 2 and 3). In case 2 the only evidence was polyuria, which occurred late in the disease. At necropsy it was observed that the tumor had implanted itself widely over the base of the brain and that a large portion of the posterior lobe of the pituitary body had been destroyed by a metastatic lesion. In case 3 the patient obviously was suffering from hypopituitarism. In this case the polyuria appeared early in the course of the disease and subsided after partial removal of the tumor, which was situated posterior to the optic chiasm. Because of the widespread metastasis and implantation, it is, of course, impossibile to make injury of any single structure responsible for the polyuria. Similar cases, in which implants on the floor of the third ventricle were associated with diabetes insipidus, have been reported by Horrax and Bailey, Fulton and Bailey,[9] Stringer[10] and Friedman and Plaut.[11] In the case reported by Stringer implants were seen only in the tuber cinereum.

An interesting feature was the complete absence of the syndrome macrogenitosomia praecox in the 2 cases in which the patients had not reached the age of puberty. In 1 of these cases (not reported) a girl aged 7 years had a spongioblastic pinealoma. The absence of precocious puberty in this case is not surprising because of the rarity of signs of this disorder in girls who have pineal neoplasms. Berblinger, in 1926, said that there was no known case in which a female with macrogenitosomia praecox had been found to have a pineal neoplasm at necropsy. In the other case (not reported) in which the patient had

9. Fulton, J. F., and Bailey, P.: Tumors in the Region of the Third Ventricle: Their Diagnosis and Relation to Pathological Sleep, J. Nerv. & Ment. Dis. **69:** 1-25 (Jan.); 145-164 (Feb.); 261-277 (March) 1929.

10. Stringer, S. W.: Diabetes Insipidus Associated with Pinealoma Transplant in the Tuber Cinereum, Yale J. Biol. & Med. **6:**375-383 (March) 1934.

11. Friedman, E. D., and Plaut, A.: Tumor of the Pineal Gland (Pinealocytoma) with Meningeal and Neural Metastases, Arch. Neurol. & Psychiat. **33:** 1324-1341 (June) 1935.

not reached the age of puberty, a boy aged 10 years had a pineal ependymoma, but there was no evidence of precocious puberty.

In none of the other 4 cases in which a complete necropsy was performed was there any evidence of hyperplasia of either the tubular or the interstitial cells of the testis.

SURGICAL TREATMENT OF PINEALOMAS

Tumors of proved pineal origin are rare. This is fortunate, as these neoplasms are extremely difficult to treat satisfactorily. As far as is known, the only way to obtain a cure in a case of pinealoma is complete surgical extirpation of the tumor. The pineal body is so situated that any surgical attack on neoplasms arising therefrom is fraught with many hazards. By the time the tumor has reached sufficient size to produce symptoms and signs that will enable one to make a diagnosis, the mass may be encroaching on the midbrain, projecting into the third ventricle or distorting the veins of Galen, which are essential for the patient's survival. By pressing downward on the aqueduct of Sylvius, the tumor may cause partial or complete obstruction to the outflow of fluid from the lateral and third ventricles.

When a diagnosis of pinealoma has been made, it is necessary to decide on the type of therapy, that is, whether direct surgical attack on the tumor, radiation therapy or palliative subtemporal decompression before roentgen or radium therapy over the pineal region is preferable.

If direct surgical attack is selected, one of several approaches may be used. It is our opinion that no single approach is entirely suitable in all cases. The operation should be elected that best fits the particular situation. The transcallosal approach of Dandy [12] is preferred by many for attacking tumors in the third ventricle. Dandy has reported the successful performance of operations by this approach. Kahn [13] has reported the successful removal of 2 pinealomas by means of this approach. The upright position (Adson) facilitates exposure of the pineal region, tentorial notch and brain stem in operating for pineal tumor and other lesions in the posterior end of the third ventricle.

The transventricular approach of Van Wagenen [14] is particularly applicable in cases in which a large extension of the tumor into the

12. Dandy, W. E.: An Operation for the Removal of Pineal Tumors, Surg., Gynec. & Obst. **33**:113-119 (Aug.) 1921.

13. Kahn, E. A.: Surgical Treatment of Pineal Tumor, Arch. Neurol. & Psychiat. **38**:833-842 (Oct.) 1937.

14. Van Wagenen, W. P.: A Surgical Approach for the Removal of Certain Pineal Tumors: Report of a Case, Surg., Gynec. & Obst. **53**:216-220 (Aug.) 1931.

third ventricle is associated with blockage of the aqueduct of Sylvius and extensive internal hydrocephalus.

Horrax [15] recently described a technic for the removal of unusually large pinealomas. This procedure has much to commend it, although a large part of a more or less normal cerebral hemisphere must be sacrificed. This operation, of course, is not recommended for use in all cases, but the sacrifice of a portion of the brain that is relatively silent in order to save a life is a just and fair exchange.

The transfrontal approach was employed successfully in 1 of our cases (case 3), although it did not permit complete removal of the tumor; we believe that the case is rather unique. The subtotal removal of the tumor and subsequent irradiation relieved the patient's symptoms, although he returned later because of metastasis or implants in and along the cauda equina.

In 1 of our cases (not reported) a combined approach, or two stage operation, permitted complete extirpation of the tumor (proved at necropsy), although the patient failed to survive the second operation. At the first operation the left occipital lobe was retracted laterally, and a partial transcallosal removal of the pinealoma was performed. Three days later the remainder of the encapsulated tumor was removed by a suboccipital approach. The wound was being closed when the patient died suddenly. Although the operation cannot be considered a success in this instance, its possible usefulness is suggested.

HISTOLOGIC FEATURES

All our cases can be classified in three groups, according to the histologic structure of the tumors. The first group includes 2 cases in which the histologic picture of the neoplasm revealed a predominating gliomatous structure. The tumors of this group resembled the so-called spongioblastic pinealoma described by Horrax and Bailey. This group has been under fire, and some workers, particularly Globus and Silbert, have refused to recognize gliomas as arising in the pineal body. Similar neoplasms have been described, however, by Berblinger, Zeitlin,[16] Haldeman and others. The histologic appearance of these neoplasms suggests the necessity of such a group. A tumor of this type was present in case 1.

The second group includes cases in which the histologic appearance of the tumor more or less resembled the various stages of development of the normal pineal body. This type of tumor has been ably studied

15. Horrax, G.: Extirpation of a Huge Pinealoma from a Patient with Pubertas Praecox: A New Operative Approach, Arch. Neurol. & Psychiat. **37:** 385-397 (Feb.) 1937.

16. Zeitlin, H.: Tumors in the Region of the Pineal Body: A Clinicopathologic Report of Three Cases, Arch. Neurol. & Psychiat. **34:**567-585 (Sept.) 1935.

and described by Globus and Silbert. According to these investigators, tumors of the pineal body "may be traced to embryonal rests that may recapitulate any of the stages in the development of the pineal and thus assume histologic characters paralleling any phase in the life history of the gland." In 5 of our cases the histologic sections of the tumors resembled phases in the development of the normal pineal body.

In case 2 and in 2 other cases which are not reported the histologic appearances of the neoplasms were suggestive of the pineal body of an infant of about 2 months. Histologically, the tumor seen in case 3 was similar to the pineal body of an infant of 9 months. In another case, which is not reported, the histologic appearance of the neoplasm resembled somewhat that of the pineal body of the adult.

In saying that these neoplasms resembled or were similar to various stages of development of the pineal body, we do not necessarily mean to imply an origin from embryonic rests. The arguments for and against this theory of neoplastic origin would be out of place in this paper. There were, of course, certain differences in the histologic appearance which served to distinguish the neoplasms of this type from the various stages of development of the normal pineal body. The parenchymal cells of the tumor were larger and possessed large nuclei which had immense, violet-staining nucleoli. Mitotic figures were also more numerous in the tumor, and there were multinucleated, syncytial masses of cytoplasm. These are evidences of neoplasia rather than characteristics of the developing pineal body.

Cases 2 and 3 were in many respects the most remarkable in this series. To date, we have been able to find only 3 similar cases in the literature: 1 reported by Berblinger in 1926, 1 reported by Fulton and Bailey in 1929 and 1 reported by Friedman and Plaut in 1935. The anatomic similarity between the tumors in our cases and that in the case reported by Berblinger was striking. In the case reported by Berblinger there was metastasis to the spinal cord and the cauda equina. This was also true in case 3, but was not ascertained in case 2. In case 2 only the brain was sent us, since permission to examine the spinal cord could not be obtained. In this case there were numerous gross implants on the walls of all the ventricles, which were not mentioned in Berblinger's report. Similar tumors were present, however, in the case described by Fulton and Bailey. The case reported by Friedman and Plaut is interesting in that there was no gross tumor of the pineal body or pineal region; there was metastasis to the cranial and spinal nerves, however, and tumor cells were seen about the cerebral veins. Horrax and Bailey and Stringer have reported cases in which the implants were limited to the third ventricle. In Stringer's case the implant was observed only in the tuber cinereum. The case

reported by Alajouanine, Thurel and Oberling [17] should be mentioned in this connection. The tumor which they described was situated in the region of the pineal body, and metastasis was seen only in the spinal cord. They expressed doubt concerning the origin of the tumor. Microscopically, the neoplasm resembled a medulloblastoma. They were unable to identify the pineal body.

The third group includes cases in which the tumors were classified as pineal ependymomas. The first examination of these neoplasms strongly suggested three possibilities in diagnosis: metastatic adenocarcinoma, pineal teratoma and, finally, pineal ependymoma. A complete necropsy in case 4 ruled out the possibility of a metastatic lesion. In another case (not reported), in which only the head was examined at necropsy, the presence of such a lesion was possible, but unlikely, as the patient was only 10 years of age. In still another unreported case, a metastatic tumor was likewise unlikely, since the patient was only 23 years of age and there were no signs or symptoms of a tumor elsewhere in the body.

In this group a diagnosis of teratoma could not be supported because of the impossibility of demonstrating derivatives of all three germ layers and because there was absence of any attempt to form organs. As the photomicrographs show, there was a loose mesenchymal interstitial tissue which might have been assumed to be of mesodermal origin, and there were groups of epithelial cells which in some regions revealed a glandular structure and produced mucus. These might have been considered endodermal in origin. If one stopped the investigation at this point the diagnosis of a teratoid or mixed tumor might appear justifiable. Further examination showed, however, that not all the epithelial cells possessed a glandular arrangement and that in some regions there were groups of large cells arranged in solid masses and cords; these undoubtedly were neoplastic pineal parenchymal cells (fig. 7). There were many stages between the arrangement of the neoplastic parenchymal cells and that of the cells lining the glands. In a few of the cells arranged in solid cords and masses intracellular mucus was actually demonstrated. It is probable, therefore, that these cells and the acinar cells are fundamentally alike and indicate merely different histogenetic phases.

The resemblance of these tumors to ependymomas is striking. The glandular arrangement of the parenchymal cells is like that of the epithelial ependymomas, while the production of mucus finds its only counterpart in the tumors designated as papilloma choroideum and

17. Alajouanine, T.; Thurel, R., and Oberling, C.: Etude séméiologique et évolutive d'un syndrome de Parinaud mésocéphalique: Neurospongiome de la région pinéale avec métastases médullaires, Rev. neurol. **1**:227-232 (Feb.) 1934.

myxopapillary ependymoma. As Kernohan and Fletcher-Kernohan [18] have shown, intracellular production of mucus is a characteristic of papilloma choroideum and occasionally is also seen in the myxopapillary ependymoma. The glandular arrangement, the loose myxomatous stroma and the production of mucus are features which show the close relationship between this group of tumors of the pineal body and ependymomas.

The feature which distinguishes pineal ependymomas from pure ependymomas is the presence of large cells having the characteristic appearance of pineal parenchymal cells. The fact that no trace of a normal pineal body could be seen in these tumors is also in favor of a pineal origin. The presence of numerous mitotic figures, giant nuclei and giant cells is indicative of a high degree of malignancy.

Tumors similar to these have been described by Marburg under the term *zusammengesetzte Geschwülste*. According to him tumors of this type are arranged in three sheaths, lying one above another. The outer sheath contains pineal cells in somewhat irregular arrangement. Ependymal cells are the chief constituent of the second sheath but are mixed, nevertheless, with cells of the choroid plexus. The ependymal cells form round, long, tubular or glandular cavities that are lined with epithelium. The lowest sheath consists of glia cells and fibers. Marburg emphasized that this tumor consists of various tissues derived from a single germ layer and arises from a region where these types of tissues are in close relation to one another. Although all the elements described by Marburg were present in our cases, their arrangement in sheaths was not distinct and sometimes could not be made out.

In cases reported by Turner,[19] Ogle,[20] Pappenheimer,[21] Rorschach,[22] Schminke,[23] Derman and Kopelovitch [24] and Friedmann and Scheinker,[25]

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18. Kernohan, J. W., and Fletcher-Kernohan, E. M.: Ependymomas: A Study of 109 Cases, A. Research Nerv. & Ment. Dis., Proc. (1935) **16**:182-209, 1937.

19. Turner, F. C.: Spindle-Cell Sarcoma of the Pineal Body, Containing Glandular and Carcinomatous Structures, Tr. Path. Soc. London. **36**:27-35, 1885.

20. Ogle, C.: Tumor of Pineal Body in a Boy [case 2], Tr. Path. Soc. London **50**:6-12, 1899.

21. Pappenheimer, A. M.: Ueber Geschwülste des Corpus pineale, Virchows Arch. f. path. Anat. **200**:122-141 (April 2) 1910.

22. Rorschach, H.: Zur Pathologie und Operabilität der Tumoren der Zirbeldrüse, Beitr. z. klin. Chir. **83**:451-474 (April) 1913.

23. Schmincke: Ueber die Teratome der Zirbeldrüse, München. med. Wchnschr. **61**:2043-2044 (Oct. 6) 1914.

24. Derman, G. L., and Kopelovitch, M. A.: Zur Kenntnis der Zirbeldrüsengewächse (Ein seltener Fall von Neuroglioma ependymale embryonale gl. pinealis), Virchows Arch. f. path. Anat. **273**:657-662, 1929.

25. Friedmann, R., and Scheinker, J.: Ein Fall von Neuroepitheliom der Zirbeldrüse, Monatschr. f. Psychiat. u. Neurol. **89**:81-96 (July) 1934.

the tumors were similar to pineal ependymomas. Pappenheimer likewise observed the transition of the acinar arrangement of the ependymal cells into the solid strands. He noticed a striking similarity between these cells and fetal ependymal cells. He called the tumor an ependymal neuroglioma. Schminke, likewise, noted transitions to ependymal cells in his second case, but called the tumor a teratoma. It is possible that many of the so-called mixed or teratoid tumors described in the literature are actually neoplasms of the type here called pineal ependymoma.

The concept of the close relationship between pineal neoplasms of this type and ependymomas finds support also in the extensive embryologic studies of Marburg, Tilney and Warren and Globus and Silbert. These workers found that the pineal body arises first as an evagination of the primary vesicle. According to Tilney and Warren, lateral diverticula appear later and give rise to many follicles. These authors said that the lumens of the follicles in the human embryo are smaller than those of birds and that they ultimately are obliterated; finally, there are solid follicles surrounded by connective tissue and vessels. Globus and Silbert have observed the tubular arrangement of pineal cells in fetuses as old as 5½ months.

In the embryo, then, there is a close relationship between the lining of the primary vesicle (ependyma?) and the pineal body. A glandular or follicular arrangement of the cells is apparently a characteristic of the embryonic pineal body and also a feature of certain pineal neoplasms.

If one groups together the neoplasms in the cases in groups 2 and 3, since they all arose from the parenchymal cells of the pineal body, one has a series of pinealomas which histologically resemble various stages in the development of the pineal body. From this point of view, the spongioblastic pinealomas of group 1 might be placed in a separate category. These neoplasms apparently arose from the neuroglial tissue of the pineal body. In the remaining cases, the tumors, although differing widely in histologic appearance, might be placed together in a single group, as they arose from the parenchymal tissue of the pineal body.

SUMMARY AND CONCLUSIONS

Ten cases of pineal neoplasm have been seen at the clinic in twenty-three years. In 3 of the cases localizing signs were absent. The syndrome macrogenitosomia praecox was not observed. The objective neurologic findings were based on disturbances of the oculomotor apparatus, the pyramidal tracts and the cerebellum and its tracts.

Histologically, the cases were divided into three groups. The first group included cases in which the tumors arose from the neuroglial elements, or the spongioblastic pinealomas. The second group consisted of cases in which the tumors were pinealomas resembling stages

in the development of the normal pineal body. Two of the neoplasms in this group were particularly interesting, as they had metastasized to various parts of the central nervous system. The third group included cases in which the tumors embryologically and histologically were closely related to the ependyma. These tumors have been called pineal ependymomas. Histologically, these neoplasms appear similar to myxopapillary and epithelial ependymomas, while in their production of mucus they resemble papilloma choroideum.

The treatment of pineal tumors carries a high mortality, and the results of therapy at present are unsatisfactory. Progress is being made, and a brighter future is anticipated.

ANATOMIC RELATIONS OF CEREBRAL VESSELS AND PERIVASCULAR NERVES

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Previous work on pial and intracerebral blood vessels has demonstrated occasional perivascular nerves. By use of a new technic,[1] it has been possible to demonstrate them in far greater numbers than was hitherto suspected and to give a more complete account of their morphologic character. It has been possible to determine the relation of the number of perivascular nerve fibers to the size of vessels throughout the cerebral cortex. It has also been possible to show that the walls of cerebral blood vessels are not lacking in muscular elements, as has been stated.

Historically, the first mention of perivascular nerves to peripheral vessels was made on gross observation by Willis (1664).[2] Descriptions of such structures on pial vessels were not given until Purkinje [3] (1845) described in detail perivascular nerves accompanying the arteries in the pia of the spinal cord, cerebellum, pons and cerebrum. He noted that over the cerebrum these fibers seem to be more closely applied to the vessels than elsewhere in the central nervous system and that they could be followed to vessels of the second and third orders. He also described similar fibers in the corpus striatum and geniculate body which he said, but could not prove, accompanied vessels.

Nothing more was done with respect to the perivascular nerve supply to cerebral vessels until the latter part of the nineteenth century. At this time Gullard,[4] Obersteiner,[5] Morrison,[6] Huber,[7] Hunter [8] and

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2. Willis, T.: Cerebri anatome: Cui accessit nervorum descriptio et usus, Londoni, J. Flesher, 1664.

3. Purkinje, J.: Arch. f. Anat., Physiol. u. wissensch. Med., 1845, p. 281.

4. Gullard, G. L.: (*a*) Rep. Lab. Roy. Coll. Physicians **6**:55, 1897; (*b*) Brit. M. J. **2**:780, 1898.

5. Obersteiner, O.: Arb. a. d. Inst. f. Anat. u. Physiol. d. Centralnervensyst. u. Wien. Univ. **5**:215, 1897.

6. Morrison, A.: Edinburgh M. J. **4**:413, 1898.

7. Huber, C. G.: J. Comp. Neurol. **9**:1, 1899.

8. Hunter, J.: J. Physiol. **26**:465, 1900.

Robertson [9] wrote on the nerve supply of cerebral vessels. Of these, Huber contributed most. He described medullated and nonmedullated fibers on pial vessels forming two plexuses, one above and one beneath the adventitia. He expressed the belief that the coarse medullated fibers were sensory and the thin nonmedullated fibers motor.

During the same period Benedict,[10] Rohnstein [11] and Bielowssen [12] described connections of certain cranial nerves with the perivascular nerves of the arteries at the base of the brain and the choroid plexus. Benedict described a "straplike" bundle arising from multipolar cells in the restiform body and in the medulla and running to the choroid plexus of the fourth ventricle. He termed this the thirteenth cranial nerve.

From 1900 to 1922, when Stöhr [13] initiated the renaissance in this study, cerebral circulation was considered by physiologists as an entirely passive affair dependent on fluctuations in blood pressure. Stöhr, with the aid of refined silver technic, made an exhaustive study of the vegetative nervous system. He described an abundant perivascular nerve supply to the pial blood vessels. He found, as had Huber, that this supply was made up of coarse and fine fibers forming plexuses above and below the adventitia. He expressed the belief that the inner plexus was just above the media. He described nerves accompanying the capillaries in a loose fashion, which sent occasional very fine fibers to the capillary walls, where they terminated in "bulb-like" endings. He described endings of the sensory type, as well as connections of the cranial nerves to the perivascular nerves of the pia and choroid plexus. He stated definitely that such perivascular nerves do not exist on intracerebral vessels and can be observed only on pial vessels. Hassin [14] expressed the same opinion. After this study appeared those of Clark,[15] Dowgjallo,[16] Grigorgian,[17] Chorobski and Penfield,[18] Kurusu

9. Robertson, W. F.: Scot. M. & S. J. **4**:23, 1899.

10. Benedict: Virchows Arch. f. path. Anat. **57**:395, 1873.

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12. Bielowssen: Material zur Anatomie der Gefässnerven der Menschen, Dissert., Kharkov, 1888.

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14. Hassin, G.: A. Research Nerv. & Ment. Dis., Proc. **9**:437, 1928.

15. Clark, S. J.: J. Comp. Neurol. (*a*) **47**:1, 1928; (*b*) **48**:247, 1929; (*c*) **53**: 129, 1931; (*d*) **60**:21, 1934.

16. Dowgjallo, N. D.: Ztschr. f. Anat. u. Entwcklngsgesch. **97**:9, 1932.

17. Grigorgian, I.: Ztschr. f. mikr.-anat. Forsch. **28**:418, 1932.

18. Chorobski, J., and Penfield, W.: Cerebral Vasodilator Nerves and Their Pathway from the Medulla Oblongata, with Observations on the Pial and Intracerebral Vascular Plexus, Arch. Neurol. & Psychiat. **28**:1257 (Dec.) 1932.

and Hamada [19] and Penfield.[20] Of these, Clark carried the investigation further on the deep vessels. He described structures on the vessels deep in the medulla and spinal cord which were similar to those observed on the pial vessels. These nerves he showed to be continuations of those on the pial vessels. He expressed the belief that the fibers ended in relation to the smooth muscle cells of the vascular wall.

Penfield, taking cognizance of the work of von Kölliker,[21] demonstrated fine fibers on intracerebral blood vessels from various parts of the cerebrum in man and animals. He asserted that these fibers were abundant; he observed two complexes, one above the adventitia and one just above the media. He demonstrated nerve endings which he said were sensory.

With the knowledge, then, of a perivascular nerve supply to both pial and intracerebral arteries, I undertook this work to determine the actual richness of the supply and to detect any significant difference in the various portions of the cortex.

MATERIALS AND METHODS

The vessels for this study were obtained from autopsy material, the patients representing a large range of age groups, extending from youth to middle life. Many vessels were studied, ranging from those 250 microns in diameter down to the smallest vessels. Vessels were obtained by the method described by Penfield,[22] that is, by dissection under a binocular dissecting microscope. Brain substance was teased away with the aid of needles, and in some instances was sucked away from the vessels with the use of a very fine-pointed glass suction tip. In this manner it was possible to obtain intracerebral vessels of the smallest size, and in many instances capillaries came away with the fine arterioles. The sleeve of pia, which has been described by Penfield as accompanying vessels into the brain substance, was dissected away. When the study was first undertaken, the Penfield modification of the Gros-Bielschowsky silver impregnation was used. This method was carried out on material fixed in a solution of formaldehyde and acetic acid. Results after the mastery of the technic were fairly uniform, but it was found that many vessels were lost in the process, owing to overprecipitation of silver.

Silver impregnation by the use of activated strong protein silver was then undertaken, with striking results. It was found that by this method no vessel was lost from overprecipitation and that it was possible to obtain clear differentiation. Strong protein silver in this instance was activated by copper. As has been pointed out by Bodian,[23] the method of fixation of tissues is of prime importance in any result which may be expected. For fresh material a combination of alcohol,

19. Kurusu, M., and Hamada, I., abstracted, Zentralbl. f. d. ges. Neurol. u. Psychiat. **59**:921, 1929.

20. Penfield, W.: Intracerebral Vascular Nerves, Arch. Neurol. & Psychiat. **27**:30 (Jan.) 1932.

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22. Penfield, W.: Am. J. Path. **11**:1007, 1935.

23. Bodian, D.: Anat. Rec. **69**:153, 1937.

formaldehyde and acetic acid was found to be most satisfactory. For old formaldehyde-fixed material it was necessary to treat with this solution before impregnation. The fixative also had the advantage of producing little change in diameter of the vessels from shrinkage. This was ascertained by measuring experimentally, through a Forbes's window, the diameter of vessels in the pia of a cat's brain (that is, the diameter of the rounded vessel). These vessels were then removed, fixed and impregnated. Measurements were again taken, and the diameter was found to be approximately the same. In the proportions used the swelling effect of the acetic acid was apparently balanced by the shrinking effect of alcohol and formaldehyde. The diameter of the vessels in life (diameter of rounded vessel)

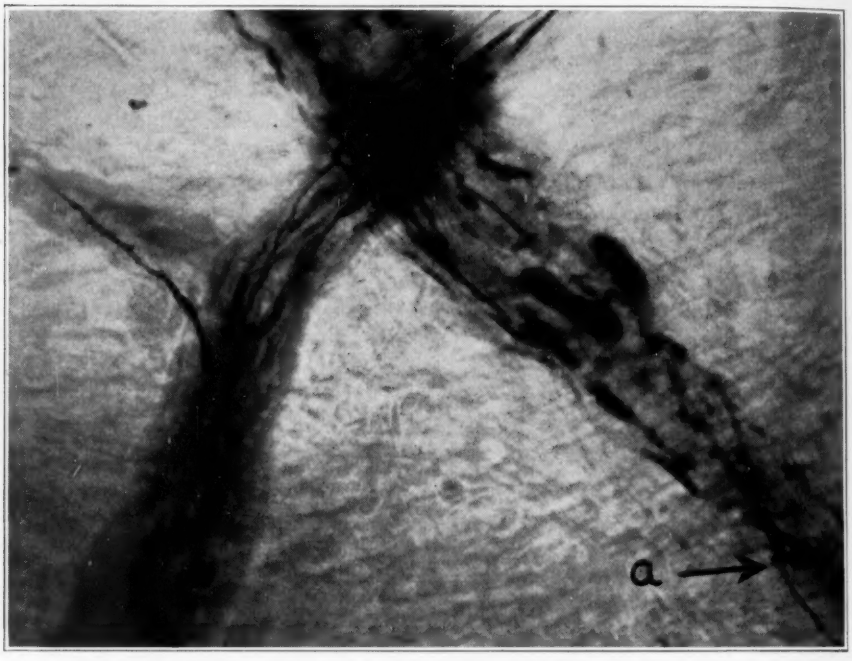

Fig. 1.—Photomicrograph showing manner in which a single fiber leaves the trunk (*a*) and the moniliform character of the fiber.

was six-tenths that of the flattened vessel under the cover slip. For example, a vessel of 100 microns under the microscope would have a diameter during life of 60 microns. All measurements of vessels in this study were thus corrected. After impregnation and reduction the vessels were cleared in oil of bergamot and mounted in balsam. Before applying the cover slip the vessels were flattened out under the dissecting microscope.

OBSERVATIONS

As described in the method, all enveloping tissue that might distort the picture was stripped from the vessels. It was found that vessels from all parts of the cerebral substance showed uniformity of structure and distribution of perivascular

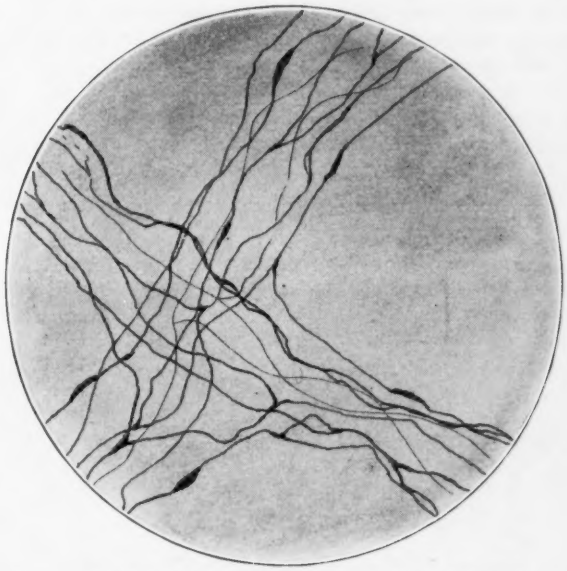

Fig. 2.—Camera lucida drawing showing complicated junction of two nerve trunks.

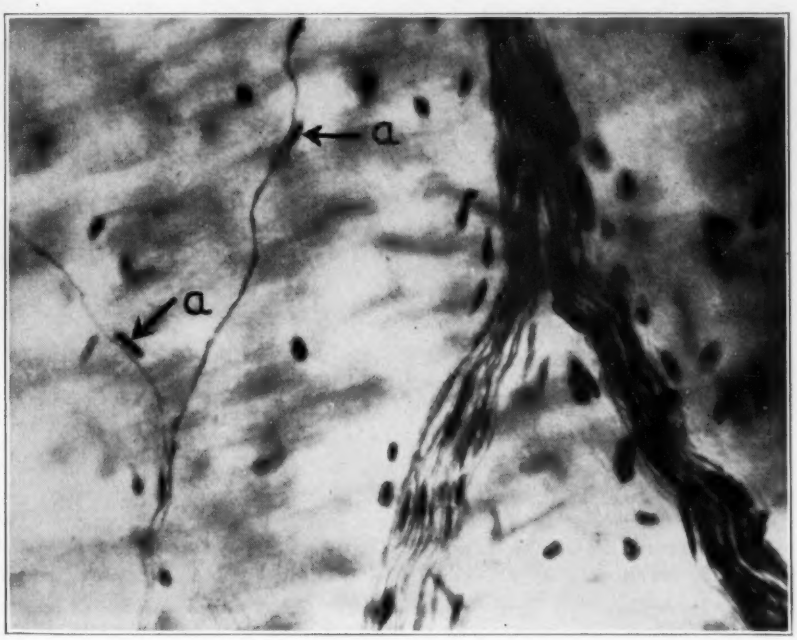

Fig. 3.—Photomicrograph showing manner of division of a nerve trunk (*a*), cells of the sheath of Schwann and moniliform type of the nerve fiber.

nerves. As has been shown by Penfield, the perivascular nerves on the intracerebral blood vessels are a continuation of the nerves on the pial vessels. These nerves were seen to enter the cerebral substance with the vessels from the pia. The nerves ran as trunks, at times with the long axis of the vessel and at others obliquely, in a winding fashion. As the trunks passed along the vessel, single fibers, or groups of two or three fibers, might be given off before the trunk itself divided into two smaller ones (fig. 1). On occasion the single fibers could be traced for long distances, only to rejoin the mother trunk. From these single fibers small collaterals could be seen to break off.

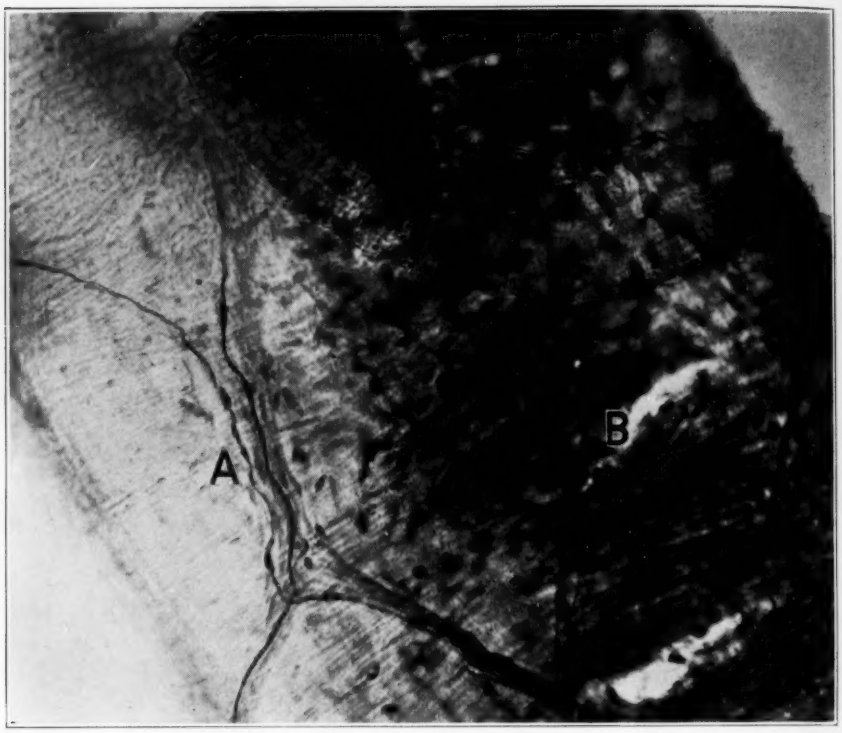

Fig. 4.—Nerves (*A*), in focus, lying in the adventitia, and similar nerves (*B*) out of focus, lying just outside the media.

Complicated junctions between nerve trunks were observed (fig. 2). In these junctions fibers were seen passing from one trunk to the other, to continue with the second in its course. Other fibers were observed to continue with their own trunk, but at the point of intersection gave off a branch at right angles which joined the second trunk. At these points was seen condensation of fiber material, such as occurs at all fiber divisions. This will be described in detail later. As has been intimated, the nerve trunks divided into two smaller ones (fig. 3). These smaller trunks, in turn, passed through the same process as the large trunks, until the entire structure was reduced to its lowest common denominator.

The location of the nerve fibers was found to correspond with that described by Huber, Stöhr, Penfield and others in that there were two complexes, one in the adventitia and one just outside the media (fig. 4). The complex in the adventitia was made up of the trunks with their side branches. By branching and rebranching, these branches formed what was thought to be a true plexus. The inner complex, the one just outside the media, was composed of nerves penetrating from the adventitia. Here, again, the nerve trunks passed through the same process of division as those in the adventitia.

The network formed by the fine fibers of the inner complex was much more complicated and was richer than that seen in the adventitia. Here, as is well shown in figure 5, there were branching and rebranching of single fibers, which joined one another, thus forming a network (fig. 6). From this structure, on

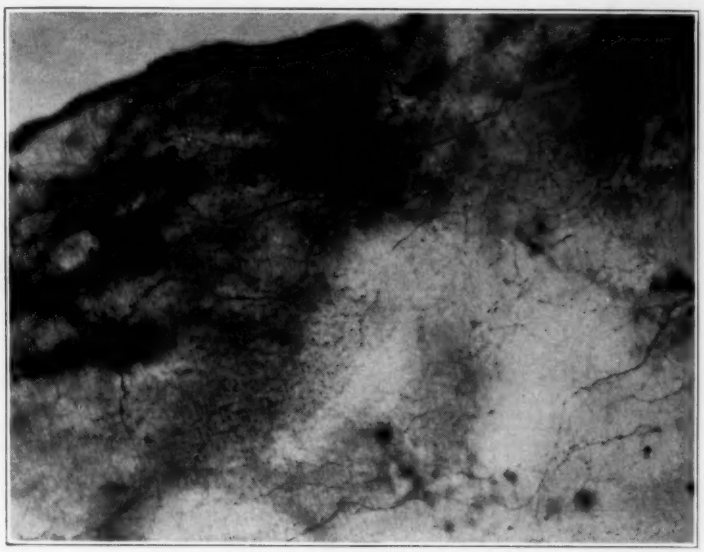

Fig. 5.—Fine nerve complex lying just outside of the media.

occasion, fine fibers could be seen penetrating the media. As a result of study of vessels that are split so that only the thickness of one wall is seen, it is believed that some of these fine penetrating fibers end in a free manner like the hairs of a horse's tail (fig. 6).

The structure of these nerve fibers was found to correspond in every way with those described by other investigators. That the structures described are nerve fibers, and not strands of connective tissue or other supportive material, is adequately proved, in my opinion, by three main features, clearly shown in photographs, namely: (1) The fibers are moniliform; (2) each fiber until it becomes a fine thread is provided with a sheath; (3) neurilemmal (sheath of Schwann) nuclei are consistently and uniformly demonstrated.

It was demonstrated that when a nerve fiber divides there is a condensation of fiber material. This condensation forms a triangular mass, the fibers taking

departure from the apexes. This structure has been claimed by Jones [24] to represent a possible nucleus, but no evidence to substantiate this opinion was obtained in this study. It is possible that what he called the cell outline is merely the dividing of the nerve sheath. Figure 7 shows this type of division, both in an actual photograph and in a camera lucida drawing.

Nerve fibers of the type described were demonstrated consistently on intracerebral blood vessels of diameters as small as 10 microns. Figure 8 represents such a vessel.

RELATION OF NUMBER OF PERIVASCULAR NERVE FIBERS TO SIZE OF VESSELS

An extremely rich and consistent perivascular nerve supply to the vessels of the cerebral substance having been demonstrated, an attempt was made to arrive

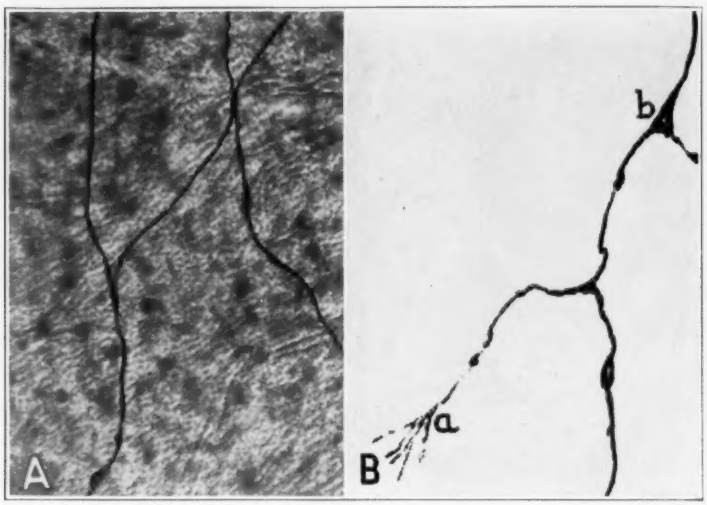

Fig. 6.—*A*, high power photomicrograph illustrating manner in which single fibers join one another in the complex lying just outside the media. *B*, camera lucida drawing showing (*a*) manner in which a fine single fiber disappears into the media, like a horse's tail, and (*b*) condensation of fiber substance at the point of division.

at an estimate of the number of fibers per unit length of vessel for vessels of different diameters. For the purpose of this study, vessels ranging in size from 250 microns to that of a capillary were chosen. The vessels were first grouped according to the area of the cortex from which they were taken. These areas I have termed I, II, III and IV (fig. 9). For the most part, they correspond to the frontal, parietal, occipital and temporal regions, except that I have included in area II the precentral gyrus. The vessels were grouped in turn according to diameter, thus: 250 to 225 microns; 225 to 200 microns, down to 25 microns or less. With this as a groundwork, fiber counts were made.

24. Jones, I.: Am. J. Anat. **58**:227, 1936.

Counts were made as follows: The unit length of vessel was arbitrarily taken as 1 mm. The fibers in the main nerve trunk were counted. As the sum of the number of fibers in each of the two branches of a nerve trunk was found to be greater than the number in the parent trunk, owing to division of individual fibers, the difference between this sum and the number of fibers in the main trunk was added to the number in the main trunk; i. e., if the main trunk contained 40 fibers and the two branches contained 25 and 20 fibers, respectively, the number of fibers

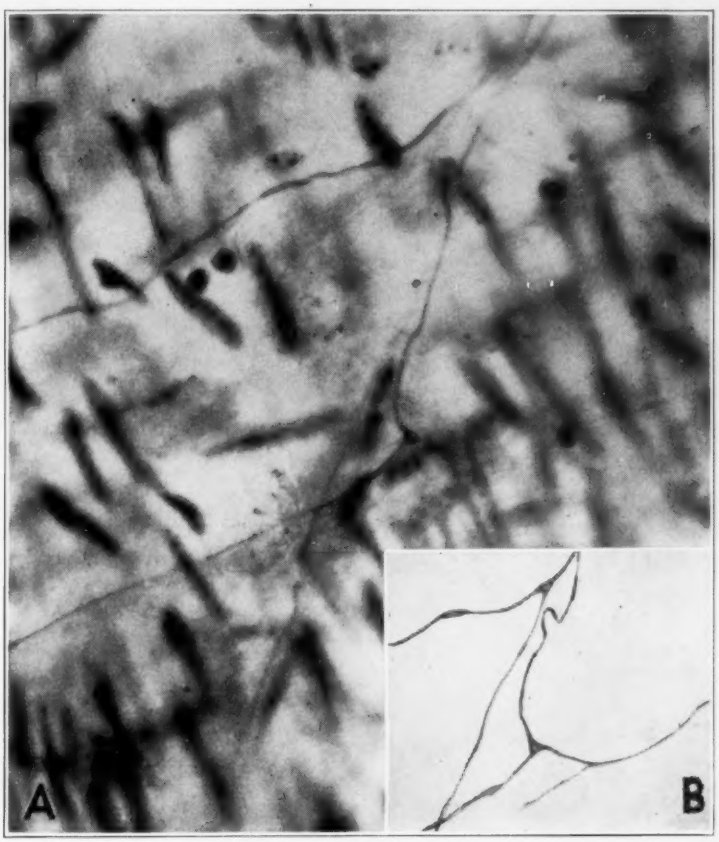

Fig. 7.—*A*, high power photomicrograph showing manner in which single fibers divide, condensation of fiber material at the point of division and moniliform character of single fibers. *B*, camera lucida drawing of the same fiber.

for the vessel would be (45—40) + 40, or 45. To this number was also added any single fiber that could be followed at least 100 microns.

Counts were thus carried out on vessels of the stated diameters from the four areas of the cerebral cortex, as shown in figure 9. No significant difference in the number of fibers per size of vessel was observed in these areas. The numbers

are indicated graphically in the chart (fig. 10). It will be noted that the number of fibers per size of vessel decreases in an orderly fashion with the size of the vessel.

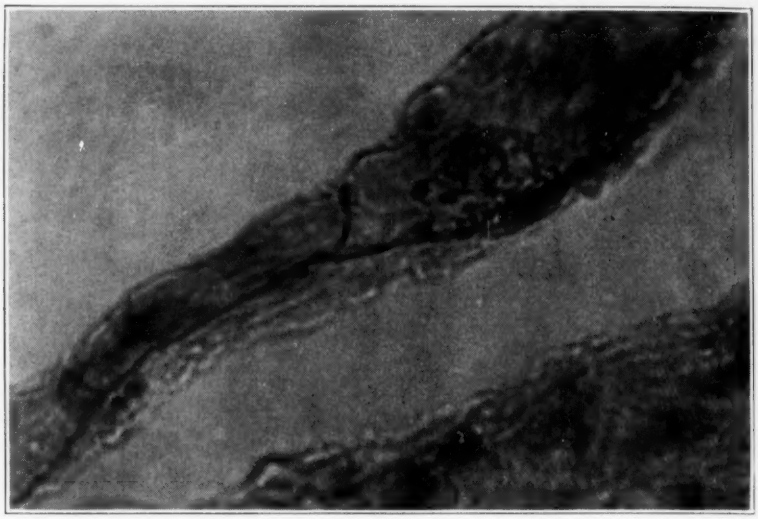

Fig. 8.—High power photomicrograph showing a nerve fiber on a vessel 10 microns in diameter.

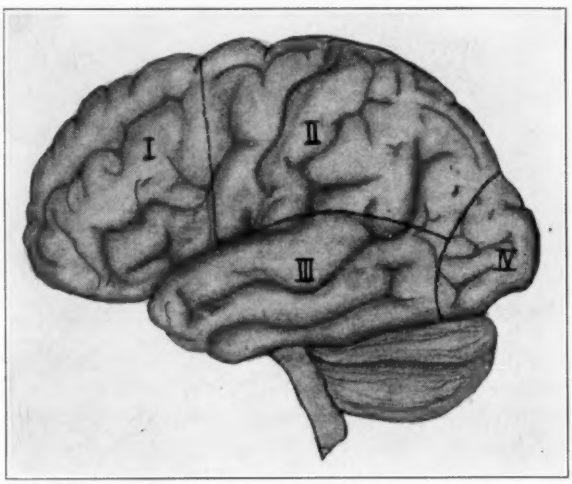

Fig. 9.—Areas from which vessels were removed for comparison of fiber counts.

As no significant difference could be demonstrated in the fiber counts from all portions of the cortex, it was considered justifiable to determine the mean of counts for all vessels of a given size as a standard. By this method it was found

that the mean count of fibers ranged from 86 fibers per millimeter of vessel length for vessels 250 microns in diameter to 1.8 fibers per millimeter of vessel length for vessels 25 microns or less in diameter. In order that accuracy of counts in any

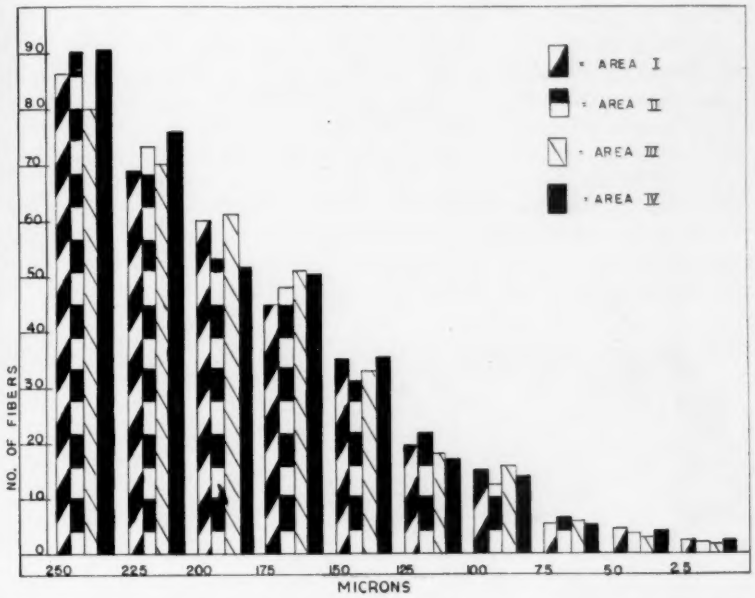

Fig. 10.—Graph illustrating mean fiber counts from various portions of the brain. Abscissas indicate diameters of the vessels expressed in microns; ordinates, the number of fibers per unit of vessel length.

Number of Fibers Per Unit Length of Vessel and the Standard Error of the Mean

Diameter of Vessels, Microns	Mean No. of Fibers Per Vessel	Standard Error of Mean
250-225	86	±9.696
225-200	72.4	±8.812
200-175	56.5	±7.894
175-150	49	±7.761
150-125	34	±7.628
125-100	19.3	±4.990
100-75	14.4	±3.927
75-50	5.4	±1.566
50-25	4	±1.408
25 and below	1.18	±0.472

future study might be assured, the standard error of the mean for each group was determined. For this impregnation method, then, the limits of error in any single fiber count for a vessel of given size were determined. A tabulation of these values is given in the accompanying table.

MUSCLE CONTENT OF THE MEDIA

In recent literature certain reports have appeared concerning the muscle content of the walls of intracerebral blood vessels, in particular, the report of Baker.[25] He expressed the belief that vessels in the cerebral cortex under 70 microns and those in the basal ganglia under 50 microns were composed of collagenous tissue and had little, if any, muscle. His studies were carried out on sections cut from strips of brain tissue and stained by various methods.

In the course of this study it was noted that the smooth muscle cells were readily and clearly impregnated with the silver. By varying the time of impregnation and reduction, the nuclei could be made to stand out in bold relief. Vessels were obtained by the dissection method as described and were impregnated. The results of the investigation follow. The walls of cerebral blood vessels were observed to be thinner than those elsewhere in the body, but had a definite media composed of smooth muscle. This muscle was arranged in an outer circular and an inner longitudinal coat. This arrangement persisted down to arteries of from

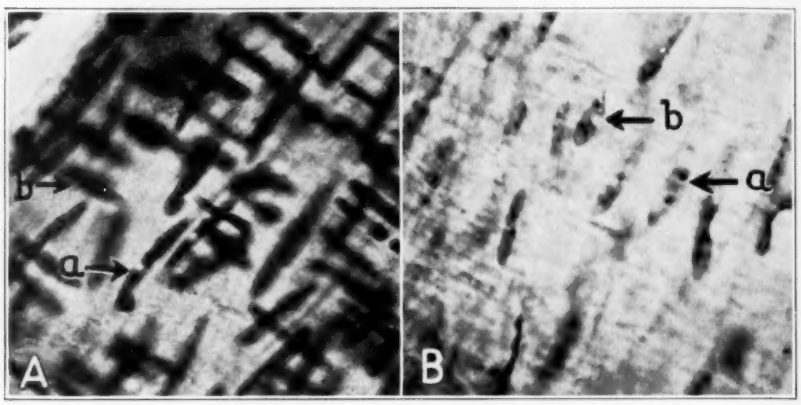

Fig. 11.—*A*, (*a*) diplosome in the nucleus of a smooth muscle cell of the longitudinal layer, and (*b*) smooth muscle cell of the circular layer. *B*, (*a*) a smooth muscle nucleus with dots of concentrated chromatin substance, and (*b*) dots of chromatin material, as well as a diplosome.

25 to 20 microns. From this point the circular coat was gradually lost; the longitudinal coat continued through the precapillaries.

That these cells were smooth muscle cells was clearly shown by their nuclei. These nuclei were oval, with a granular protoplasm. Within each nucleus there were seen, on an average, three dots of chromatin condensation, one as a rule at either end and one in the midportion of the nucleus. Many of the nuclei showed an area which appeared as though a bite had been taken out of the side. This, according to Maximow,[26] is a diplosome without an attraction sphere (fig. 11). I have been unable to demonstrate a nerve ending in these areas, as mentioned

25. Baker, A. B.: Am. J. Path. **13**:453, 1937.

26. Maximow, A. A., and Bloom, W.: Text Book of Histology, ed. 2, Philadelphia, W. B. Saunders Company, 1934.

by Boeke,[27] but at times within its bounds could be seen a peculiar fine structure, almost like a tangle of extremely fine thread. The significance of this I do not know. Adequate evidence, I believe, has been found of the presence of muscle in the walls of intracerebral blood vessels down to the capillaries.

COMMENT

The existence of a rich perivascular nerve supply to the intracerebral arteries having been established and an estimate of its quantity having been made, the question arises as to the part it plays in the control of cerebral circulation. It is believed that for the most part these fibers are of the motor variety (the fine "threadlike" structure). The reasons for this belief are based on anatomic [27a] and physiologic evidence.

The anatomic basis is found in the fact that the structure of the fibers corresponds in every detail with that of motor fibers observed on blood vessels elsewhere in the body. They are moniliform and are possessed of an embracing sheath, which in turn is supplied with Schwann cells. Further anatomic evidence that these fibers not merely are vestigial structures but have functional value lies in the fact that by the method used it was possible to demonstrate fibers on approximately 100 per cent of vessels impregnated. It is believed that in the few instances in which nerve fibers were not demonstrated the cause lay in the technic, and not in the absence of nerves. This is opposed to the results of Williams,[28] who expressed the belief that the nerves were vestigial. His opinion was based on the fact that, using many technics, he was able to demonstrate fibers on only 2 per cent of intracerebral vessels.

A third bit of anatomic evidence that these nerves are at least in part under the control of the sympathetic nervous system is given by the experiments of Orr and Sturrock,[29] later repeated by Talbott, Wolff and Cobb.[30] These investigators found that after unilateral cervical sympathectomy there was ipsilateral dilatation of the cerebral vascular bed. Chorobski and Penfield demonstrated a probable parasympathetic

27. Boeke, J.: (*a*) J. Comp. Neurol. **51**:299, 1930; (*b*) **56**:27, 1932; (*c*) in Penfield, W.: Cytology and Cellular Pathology of the Central Nervous System, New York, Paul B. Hoeber, Inc., 1932, vol. 1, p. 241.

27a. The words "anatomic" and "physiologic" are used in order to conform to the terminology adopted by the ARCHIVES OF NEUROLOGY AND PSYCHIATRY. The author would prefer to use the terms "anatomical" and "physiological."

28. Williams, D. J.: (*a*) The Innervation of the Cerebral Circulation in Man: An Histological Study, Thesis, University of Manchester, 1935; (*b*) Brain **59**: 175, 1936.

29. Orr, D., and Sturrock, A. C.: Lancet **2**:267, 1922.

30. Talbott, J. H.; Wolff, H. G., and Cobb, S.: Cerebral Circulation: Changes in the Cerebral Capillary Bed Following Cervical Sympathectomy, Arch. Neurol. & Psychiat. **21**:1102 (May) 1929.

element passing along the greater superficial petrosal nerve. They showed that after section of this nerve there was scattered degeneration of perivascular nerves to cerebral vessels. They, however, were able to demonstrate a fairly rich perivascular supply even after section of the cervical portion of the sympathetic chain and the greater superficial petrosal nerve. This matter is being investigated in a further study.

Physiologic evidence of the motor function of these nerves is adequately furnished by the studies of many investigators: Cobb and Finesinger;[31] Forbes, Finley and Nason;[32] Forbes and Wolff,[33] and Chorobski and Penfield. These men showed changes in caliber of pial vessels following stimulation of both the sympathetic and the parasympathetic trunks and the use of drugs. Recent physiologic work of Tinel and Ungar,[34] reported in the French literature, strongly suggests a nice balance between sympathetic and parasympathetic control of pial vessels. By use of drugs which put the parasympathetic system out of function and then injection of sympathetic stimulants, he produced constriction of pial arteries to a marked degree. It is believed that any knowledge of the reactions of pial arteries can now be applied to intracerebral arteries—from the seen to the unseen—as a similar, adequate perivascular nerve supply to intracerebral vessels has been demonstrated. A study is now in progress to determine whether there is an increase or decrease of this supply in disease.

It is believed that a definite muscular coat has been demonstrated in the walls of intracerebral arteries. This coat is made up of two layers, a circular and a longitudinal. Muscle cells have been demonstrated in vessels down to the precapillaries. This is consistent with the observation of nerve fibers, which have been demonstrated on walls of vessels as small as 10 microns in diameter.

SUMMARY AND CONCLUSIONS

1. A rich perivascular nerve supply to the intracerebral blood vessels of all sizes down to 10 microns has been demonstrated.

2. An estimate of the richness of this supply has been made by means of fiber counts on vessels of varying sizes and of unit length.

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31. Cobb, S., and Finesinger, J. E.: Cerebral Circulation: Vagal Pathway of Vasodilator Impulses, Arch. Neurol. & Psychiat. **28**:1243 (Dec.) 1932.

32. Forbes, H. S.; Finley, K. H., and Nason, G. I.: Cerebral Circulation: Action of Epinephrine on Pial Vessels; Action of Pituitary and Pitressin on Pial Vessels; Vasomotor Response in the Pia and in the Skin, Arch. Neurol. & Psychiat. **30**:957 (Nov.) 1933.

33. Forbes, H. S., and Wolff, H. G.: Cerebral Circulation: Vasomotor Control of the Cerebral Vessels, Arch. Neurol. & Psychiat. **19**:1057 (June) 1928.

34. Tinel, J., and Ungar, G.: Presse méd. **44**:169, 1936. Tinel, J.: Rev. neurol. **65**:1255, 1936.

3. It has been shown that no appreciable difference in fiber counts exists for vessels of the same caliber from various portions of the brain.

4. Nerve fibers have been demonstrated on approximately 100 per cent of the vessels impregnated.

5. Anatomic and physiologic evidence has been produced that for the most part these nerves are vasomotor, of both sympathetic and parasympathetic origin.

6. A definite muscular coat in the walls of intracerebral blood vessels extending down to the capillaries has been demonstrated.

7. The standard error of the mean of fiber counts has been determined for the method used, so as to define the limits of error in any single fiber count for a vessel of given size.

Case Reports

VITAMIN STUDIES IN CASES OF DIABETIC NEURITIS

WILLIAM NEEDLES, M.D., NEW YORK

In recent years some light has been thrown on the obscure field of the causation of various forms of polyneuritis. Previously, the occurrence of neuritis in the deficiency disease beriberi, as well as the experimental production of polyneuritis in animals on a vitamin-free diet, had pointed to the probable importance of avitaminosis in the pathogenesis of neuritis.

In 1928, Shattuck [1] suggested that polyneuritis occurring in ill nourished persons with tuberculosis, cancer, syphilis, diabetes, alcoholism and marasmus might be due to insufficiency of vitamin B and might be identical with the disease known as beriberi. The occurrence of polyneuritis in association with hyperemesis gravidarum pointed in the same direction. Until more substantial clinical evidence was forthcoming, however, such views had to remain more or less conjectural. In 1930, Wechsler [2] reported a group of cases of polyneuritis in which dietary inadequacy was definitely established and in which the patient improved promptly when a vitamin-rich diet was administered. Wechsler stressed the significance of gastric and hepatic insufficiency, and hence of inadequate absorption and utilization of foodstuffs, in cases of chronic alcoholism and arsenic and phosphorus poisoning, in which previously the emphasis had been laid almost exclusively on the toxic factor. In 1933, Wechsler [3] buttressed his argument for the importance of dietary factors by a report of additional cases of a similar import. Minot, Strauss and Cobb [4] presented further evidence for this contention when, in a study of 43 cases of alcoholic neuritis, they discovered that in 41 instances the diet appeared grossly inadequate.

These studies were of inestimable value in focusing attention on the hitherto neglected role of diet in the pathogenesis of neuritis and in cautioning that unwarranted stress had been placed on the role of "toxic" or "infectious" factors. Nevertheless, these studies were necessarily limited in one respect: the estimation of what constituted a defective diet remained at best approximate and qualitative. It could simply be noted that a person partook only of certain kinds of foods, avoiding others, or that he took a scant amount of certain articles of diet. The caloric value of the food ingested was generally neglected, and, of course, the

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1. Shattuck, G. C.: The Relation of Beri-Beri to Polyneuritis from Other Causes, Am. J. Trop. Med. **8**:529, 1928.

2. Wechsler, I. S.: Unrecognized Cases of Deficiency Polyneuritis, M. J. & Rec. **131**:441, 1930.

3. Wechsler, I. S.: Etiology of Polyneuritis, Arch. Neurol. & Psychiat. **29**: 813 (April) 1933.

4. Minot, G. R.; Strauss, M. B., and Cobb, S.: Alcoholic Polyneuritis, New England J. Med. **208**:1244, 1933.

quantitative estimation of vitamins in the diet could not as yet be considered. The next step, logically, was a more precise evaluation of these factors. This was made possible by the work of Cowgill.

It may be said, without exaggeration, that Cowgill's contribution "The Vitamin B Requirement of Man," [5] published in 1934, rendered previous studies on the subject antiquated. Cowgill demonstrated, by experimental investigations as well as by comparative studies of the diets of normal persons and of those suffering from beriberi, that human beings require a certain minimal amount of the antineuritic vitamin B_1 in order to utilize satisfactorily a given number of calories. Cowgill established the required relationship between the vitamin and the caloric intake and expressed it in the form of the vitamin-caloric ration. This was found to vary somewhat also according to the weight of the person. In persons for whom the proper proportion between the vitamin and the caloric intake did not obtain, the appearance of neuritis could be anticipated.

Soon thereafter, Jolliffe, Colbert and Joffe [6] seized on the advances made by Cowgill and utilized them in studies of alcoholic neuritis. Their investigations appeared to confirm the validity of Cowgill's formula. These authors found that in chronically alcoholic subjects with polyneuritis the vitamin B_1 intake in proportion to the total caloric intake was inadequate, while in alcoholic subjects without polyneuritis the vitamin B_1 intake was sufficient. The amount of alcohol imbibed was apparently not the decisive factor in the appearance of alcoholic neuritis.

The present paper is an attempt to approach by a similar method the problem of diabetic neuritis, the exact pathogenesis of which remains undetermined. The suggestion has been made at various times that, as the diabetic patient is likely to be on a restricted diet, avitaminosis may play a role in the development of neuritis. It was thought that it might be illuminating to go beyond vague generalizations regarding the adequacy or inadequacy of such diets and to estimate quantitatively the content of the antineuritic vitamin B_1 for diabetic patients in whom peripheral neuritis developed or who suffered exacerbation of an existing neuritis. The fact that vitamin B_1 is considered the antineuritic vitamin and that deprivation of this vitamin leads to an accumulation in the tissues of pyruvic acid—a product of carbohydrate metabolism which is considered a possible factor in the production of polyneuritis [7]—seems to lend value to the investigation of the possible role of vitamin B_1 in diabetic polyneuritis. To my knowledge, an attempt at a quantitative assay of this vitamin in cases of diabetic neuritis has not as yet been made. The following cases will illustrate the method employed.

REPORT OF CASES

CASE 1.—M. W., a saleswoman aged 40, was observed at the Mount Sinai Hospital in April 1937. She had been treated for diabetes mellitus since the age of 32. When she was first observed at the Mount Sinai Hospital in May 1933 no

5. Cowgill, G. R.: The Vitamin B Requirement of Man, New Haven, Conn., Yale University Press, 1934.

6. Jolliffe, N.; Colbert, C. N., and Joffe, P. M.: Observations on the Etiologic Relationship of Vitamin B to Polyneuritis in the Alcohol Addict, Am. J. M. Sc. **191**:515, 1936.

7. Vitamin B_1 and Pyruvate Metabolism, editorial, J. A. M. A. **107**:1893 (Dec. 5) 1936.

symptoms or signs of polyneuritis had been elicited. On subsequent observation in February 1936 neurologic signs had been noted. The pupils were small and irregular and reacted sluggishly to light. There was ataxia in the finger to nose and heel to knee tests. All the deep reflexes were diminished. There was questionable hypalgesia in the distal parts of the lower extremities. Vibratory sensation was absent in the lower extremities. The Wassermann reactions of the blood and spinal fluid were negative. An exact dietary history during the interim between the two hospitalizations could not be obtained. When seen in April 1937, the patient stated that for two months she had experienced aggravation of symptoms: She had shooting pains in the soles and the calves, a sensation "as though walking on air" and unsteadiness of gait. Glycosuria had never been adequately controlled and she had had frequent insulin reactions. Neurologic

*Values for Diet of Patient in Case 1**

Food	Gm.	Vitamin B_1 Per Gram of Food, Milli-equivalents	Vitamin B_1 Value, Milli-equiva-lents	Caloric Value	Vitamin A, Sherman Units	Vitamin C, Sherman Units
Milk	100	3.6	360	69	166	4.8
Butter	15	8	120	115	100	..
Oranges	100	5.6	560	50	15	17
Eggs	60	5.6	336	88	2,000	..
Bread	30	2	60	77	...	..
Cheese	60	2	120	140	80	..
Lettuce or tomatoes	100	5	500	20	1,330	25
Beets or squash	100	3.4	340	50	...	10
Apples	100	2.2	220	60	70	5
Bread	30	2	60	77	...	..
Meat	90	5	450	150	15	..
Potato	100	3.5	350	97	35	10
Tomatoes	100	5	500	20	1,330	25
Beets, squash or carrots	100	3.4	340	50	...	10
Bread	30	2	60	77	...	..
Totals			4,376	1,190	5,141	106.8

* The weight of the patient was 116 pounds (52.6 Kg.).
Average portions were calculated from the values of Fisher (Table of Food Values, New York, Life Extension Institute, Inc., 1914).
Vitamin B_1 values were based on those of Cowgill.[5]
Values for vitamin A and C were based on those of Daniel and Munsell (Vitamin Content of Foods, Miscellaneous Publication 275, United States Department of Agriculture, 1937).

examination at this time showed ataxia of both lower limbs; the deep reflexes were diminished; vibratory sense was diminished in the hands and at and below the level of the iliac crests; there was a level for cutaneous sensation at the tenth thoracic segment, with diminution below that point; tenderness was elicited over the muscles of the calves; the pupils were miotic, irregular and sluggish in reaction to light. The systolic blood pressure was 110 mm. of mercury, and the diastolic, 80. There was no clinical evidence of arteriosclerosis. Gastric analysis showed the presence of free hydrochloric acid.

The findings were considered indicative of peripheral neuritis, with some evidence of involvement of the spinal cord as well.

The patient had received a certain diet since October 1936, that is, for four months before paresthesias and other symptoms developed. She freely admitted an occasional indiscretion in the form of a box of biscuits, but said there had been no other deviations. This diet and its values are shown in the accompanying table.

The vitamin B_1 content of the diet was 4,376 international units, and the caloric value 1,190, yielding a vitamin-caloric ratio of 3.68. Since the required ratio for a person of the weight of this patient is 1.4, it is apparent that her diet was satisfactory in this respect. Nevertheless, progression in the polyneuritis occurred. There might arise the objection that since the glycosuria was not controlled and insulin reactions occurred, an additional factor, such as vascular changes from the insulin shocks, was responsible for the neurologic picture. Even if this is granted, it does not alter the contention that the diet was adequate in vitamin B_1 content and that vitamin B_1 deficiency was not the responsible factor.

Conclusions regarding vitamins A and C cannot safely be drawn, since the minimum requirements have not as yet been accurately determined. Thus, for vitamin A they vary from 700 to 5,600 Sherman units (1,000 to 8,000 U. S. P. XI units), while for vitamins C they ranged from 30 to 150 Sherman units (300 to 1,500 international units). For this reason, study of vitamins A and C was not extended to the other cases in this report.

CASE 2.—M. T., a housewife aged 51, entered the Mount Sinai Hospital in June 1937. The onset of her illness had occurred eight months before admission, with vague pains in the limbs and gastrointestinal discomfort. Diabetes mellitus was discovered at that time. For the past six months she had experienced vertigo and frontal headaches. Physical examination showed a blood pressure of 168 systolic and 90 diastolic, with some sclerosis of the radial arteries.

Neurologic examination showed depression of the deep reflexes, with absence of the knee and ankle jerks. There was tenderness over both calves. There were hypalgesia in the lower limbs and hyperalgesia in the upper limbs, of a glove and stocking type. Similar disturbances were present for touch and temperature. Vibratory sensation was diminished at the elbows, fingers, knees and toes. The retinal arteries appeared sclerotic. Gastric analysis showed the presence of free hydrochloric acid.

After left sphenoethmoidectomy and antrotomy the headaches and vertiginous attacks disappeared.

The patient stated that she had been "always a small eater." Her customary diet was tabulated, as in case 1, but the details may be omitted here. Study of the diet showed that she consumed about 1,100 calories daily. The vitamin-caloric ratio was 3.78. Since the required ratio for a person weighing 170 pounds (77.1 Kg.) is 1.9, it is evident that this requirement was more than adequately met in her case.

CASE 3.—S. O., a salesman aged 38, was observed for the second time at the Mount Sinai Hospital in November 1937. Diabetes mellitus had been detected about seventeen years previously. Four years prior to the present admission he had experienced pain in the calves when walking, pain in the ankles when standing and cramps in the legs during sleep. These had been alleviated by regulation of the diet and the administration of insulin.

When studied at the hospital in November 1935, he showed evidence of diabetic retinopathy. The following neurologic signs were obtained: The pupils were unequal, irregular and sluggish in reaction to light; the knee and ankle jerks were markedly reduced. There was evidence of marked peripheral sclerosis, with diminished patency of the arteries in the lower limbs. Oscillometric readings showed diminished pulsations of these vessels. The blood pressure was 120 systolic and 80 diastolic. Gastric analysis was not performed in this case. The Wassermann reactions of both the blood and the spinal fluid proved negative.

When the patient was observed for the second time in November 1937, the blood pressure was 160 systolic and 100 diastolic. There was generalized arteriosclerosis. The dorsalis pedis arteries were not palpable. Neurologically, the knee and ankle jerks could not be obtained, and the pupils were as previously reported.

The patient's diet prior to his first admission to the hospital was, in his own words, "about two times what the normal person eats," and had been for many years. His daily caloric intake was 2,150 calories and the vitamin B_1 content 4,828 international units, yielding a ratio of 2.24. The required ratio for a person weighing 115 pounds (52.1 Kg.) is 1.5.

COMMENT

Certain obstacles were encountered in the course of this study which at times rendered questionable the feasibility of carrying it through. Indeed, they may account for the reluctance of other investigators to pursue such a line of inquiry. First, the paucity of suitable material was disappointing. Although the facilities of two large institutions were at my disposal over a period of two years, only 3 cases could be obtained. The question arises whether this situation is unusual or whether diabetic neuritis in general is at present uncommon. Certain facts suggest the latter explanation. At the outpatient department of the Mount Sinai Hospital approximately 800 diabetic patients are under observation; yet diabetic neuritis is regarded as an unusual occurrence.[8] Joslin,[9] on the basis of 6,000 cases of diabetes mellitus studied, stated: "Neuritis is most uncommon among my patients." There were only 6 cases of polyneuritis in his series. Murphy and Moxon,[10] in an analysis of 827 cases of diabetes mellitus in patients from an indigent community, detected 5 cases. Kraus,[11] in a study of 700 cases, did not find a single instance of true sensorimotor polyneuritis with weakness, atrophy and electrical and sensory changes. Since estimates of the incidence of neuritis in cases of diabetes vary, according to Jordan [12] from 0.6 to 57.3 per cent, the question arises whether some observers are reporting cases of neuritis or cases of diabetes with associated vague aches and pains which are forthwith categorized as instances of diabetic neuritis. In the present study numerous cases had to be excluded because of such coincidental findings as hypertrophic spondylitis, with or without an associated sciatic syndrome, syphilis, a history of excessive indulgence in alcohol, a history of a grippal infection and, in 1 case, the administration of a spinal anesthetic just prior to the onset of neuritic phenomena.

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8. Verbal communication from Dr. Herman Lande and Dr. Herbert Pollack. They stated that they have studied 115 cases of diabetes with particular care and failed to find any instance of neuritis in this group.

9. Joslin, E. P.: Treatment of Diabetes Mellitus, Philadelphia, Lea & Febiger, 1928.

10. Murphy, F. D., and Moxon, G. F.: Diabetes Mellitus and Its Complications, Am. J. M. Sc. **182**:301, 1931.

11. Kraus, W. M.: Neurologic Causes and Effects of Diabetes, M. Clin. North America **4**:225, 1920.

12. Jordan, W. R.: Neuritic Manifestations in Diabetes Mellitus, Arch. Int. Med. **57**:307 (Feb.) 1936.

Still further restrictions were necessary. Since a possible correlation between dietary inadequacy and diabetic neuritis was being sought, it was impossible to include patients who were vague about details of their diet and patients the onset of whose neuritis could not even approximately be established in point of time. The fact that diabetic patients notoriously "cheat" and often cannot be relied on for an accurate dietary history and that in any case the amount of food ingested is only approximate were additional difficulties encountered.

It will be noted that a sample diet for a single day was utilized in the estimations. Since the diet did not vary appreciably from day to day, this procedure was thought to afford a sufficiently accurate gage of the diet as a whole.

The results thus far obtained seem to indicate that neuritis may occur in patients with diabetes when there is no inadequacy in the amount of vitamin B_1 ingested. They do not, of course, rule out the possibility of a vitamin factor in diabetic neuritis, since they tell nothing about the absorption or utilization of the ingested vitamin. For this purpose studies such as are already available in the case of vitamin C will be necessary.

It should be emphasized that the conclusions of this report are merely tentative. One reason for submitting the report is the hope that similar studies may be carried out elsewhere, where suitable material may be more abundant. It will be of great value to observe patients with well controlled diabetes for the appearance of peripheral neuritis and to see whether in any such case, regardless of the duration of the diabetes, neuritis ever develops. Such cases would be of much greater significance than those of the preinsulin era, in which, as Woltman and Wilder have suggested, starvation and cachexia may have played a role.

Meanwhile, certain evidence seems to suggest an alternative explanation for diabetic neuritis in the form of vascular disease. It is contended that diabetes mellitus is accompanied by alterations in the nutrient arteries to the nerves and that this gives rise to the neuritic manifestations. Woltman and Wilder,[13] in this connection, observed that in all but 1 of 10 cases of diabetic neuritis studied pathologically at the Mayo Clinic there was marked thickening of the intraneural vessels. They considered arteriosclerosis the factor of greatest significance in producing the lesions of the nerves. Joslin[9] stated that arteriosclerosis is demonstrable by roentgenograms in about 90 per cent of cases of diabetes of five or more years' duration. At autopsy it is observed in 70 per cent of cases in which the duration was less than five years and in all cases in which it was of five years or more. He wrote:

> The first decade of life thus far, therefore, is the only decade in diabetes immune to arteriosclerosis.

This statement must be considered in connection with the oft-cited fact concerning the rarity of neuritis in youthful sufferers from diabetes mellitus. Warren[14] found, in autopsies on 300 diabetic patients, that

13. Woltman, H. W., and Wilder, R. M.: Diabetes Mellitus: Pathologic Changes in the Spinal Cord and Peripheral Nerves, Arch. Int. Med. **44**:576 (Oct.) 1929.

14. Warren, S.: The Pathology of Diabetes Mellitus, Philadelphia, Lea & Febiger, 1930.

24 per cent had died of arteriosclerosis, although 80 per cent of the series were under 40 years of age. In 37.5 per cent of the patients whose death was due to arteriosclerosis the extremities were involved; the heart was affected in 47 per cent, and the brain, in only 2 per cent. He pointed to the fact that this marked prevalence of cardiac and peripheral arterial involvement in diabetic patients contrasts strongly with the frequency of cerebral and renal damage in nondiabetic persons. It may account, incidentally, for the greater frequency with which neuritis is associated with diabetes than with generalized arteriosclerosis, since apparently the site of predilection for the vascular changes is different in the two conditions. A comparative study of the nutrient arteries of the peripheral nerves in cases of diabetic neuritis and of arteriosclerosis to ascertain whether there is a difference in the quality as well as the extensiveness of the lesions might throw additional light on the subject.

CONCLUSIONS

1. Three cases of neuritis associated with diabetes mellitus were studied with a view to ascertaining the vitamin B_1 content of the diet. In all cases the diet was found to be adequate in this particular. Neuritis in cases of diabetes mellitus, therefore, does not appear attributable to lack of vitamin B_1 in the diet, so far as conclusions based on these few cases can be drawn.

2. Reasons are discussed for considering that vascular changes in the nutrient arteries to the peripheral nerves may be responsible for diabetic neuritis, in some cases at least.

Dr. George Baehr and Dr. B. S. Oppenheimer gave me permission to study cases in their services at the Mount Sinai Hospital.

SEROLOGIC REACTIONS IN SCHIZOPHRENIA

Prognostic Value

W. L. SHARP, M.D., ANDERSON, IND.

Examinations were made of the spinal fluid and blood of all new patients admitted to the men's division at Central State Hospital, Indianapolis, during 1932 and 1933. Examination of the spinal fluid included: Ross and Pandy tests; cell counts; the colloidal gold test, and the Wassermann, Kahn and Kline tests.

In 1932, 28 (22.3 per cent) of 125 psychotic patients admitted had typical clinical dementia praecox. Of these, 32 per cent gave positive serologic reactions as tabulated.

Patient	Serologic Reactions	Age at Onset, Yr.
L. W. H.	Ross, 1 plus; Pandy, 1 plus	18
M. S.	Kahn, 4 plus; Kline, 4 plus	25
H. J.	Pandy, 1 plus	?
P. C.	Ross, 1 plus; Pandy, 1 plus	?
R. L.	Ross, 1 plus; Pandy, 1 plus	30
W. R.	Ross, 2 plus; Pandy, 1 plus	28
H. D.	Ross, 1 plus	28
J. W.	Wassermann reaction of the blood, 1 plus; Kahn reaction, 4 plus; Kline reaction, 2 plus	21
J. T.	Ross, 1 plus; Pandy, 2 plus; colloidal gold curve, 00011/00000	34

In 1933, 35 (22.3 per cent) of 156 psychotic patients admitted had dementia praecox. Of these, 28.5 per cent gave positive serologic reactions, as shown in the following tabulation.

Patient	Serologic Reactions	Age at Onset, Yr.
L. S.	Gold curve, 0011000000	23
K. B.	Gold curve, 0011000000	20
H. D.	Ross, 1 plus	19
C. R.	Pandy, 1 plus	22
C. G.	Pandy, 1 plus	28
J. S.	Ross, 1 plus; Pandy, 1 plus; gold curve, 0011100000	34
J. C.	Gold curve, 1121100000	21
C. A.	Ross, 1 plus; Pandy, 1 plus	31
H. H.	Ross, 1 plus; Pandy, 1 plus	40
C. W.	Ross, 2 plus; Pandy, 2 plus; gold curve, 0012110000	22

Of the 1932 group of patients with dementia praecox, 19 (68 per cent) gave completely normal serologic reactions. Six of these 19 patients were discharged as improved or recovered, but the remaining 13 did not improve sufficiently to be furloughed. Similarly, in the 1933 group of 35 schizophrenic patients, 22 (71.5 per cent) were serologically normal. Eight of the 22 patients were discharged as recovered or improved, whereas the remaining 14 were unable to be furloughed.

Follow-up observation of the schizophrenic patients with positive serologic reactions revealed that all have either remained in the same mental status or have deteriorated. None has recovered. In other words, I interpret these observations to mean that all schizophrenic patients with serologic changes of any sort have a bad prognosis.

An explanation why seemingly all schizophrenic patients with any serologic changes deteriorate or remain stationary mentally is speculative. Is there irritation of the meninges, the ependymal cells of the ventricles or the choroid plexus? Since Spirochaeta pallida is the only organism known to affect brain tissue in chronic fashion over a long period, could these findings be produced by atypical congenital syphilis?

Follow-up examination of the schizophrenic patients with positive serologic reactions was made on June 30, 1938.

Patient	Mental State	Present Age, Yr.
L. W. H.	Seclusive; says outside work would make him mad; masturbates excessively; weakness and fatigability predominant	24
M. S.	Died, unimproved, in a state hospital at the age of 29	
H. J.	Discharged as unimproved on March 26, 1935	19
P. C.	Died, unimproved, in a state hospital	
R. L.	Worse; catatonic excitement; extreme negativism; flexibilitas cerea	36
W. R.	Discharged as unimproved on June 18, 1934; had written a letter to his staff physician threatening death by "a gang" unless a discharge was granted	34
H. D.	Died, unimproved, of pulmonary tuberculosis after four years in the hospital at age of 32	
J. W.	Apathy pronounced; still has delusions that a gang is after him and that the sun ruined his soul while he did garden work	27
J. T.	Died of pulmonary tuberculosis, without mental improvement, at the age of 37	
L. S.	Excessive masturbation; catatonic excitement at times, requiring restraint; at times, a hebephrenic picture	28
K. B.	Discharged, slightly improved, on June 9, 1937.	
H. D.	Apathetic; extremely lazy and without any ambition or drive, though coherent	24
C. R.	Erroneous classification; the case was one of manic-depressive psychosis	27
C. G.	Absolute mutism now, whereas he answered some questions before	28
J. S.	Discharged as unimproved	40
J. C.	Mute; nervous under hard work; stereotopy of movement; episodic laughter	26
C. A.	Discharged. Had given promise of improvement, but follow-up letter stated: There is fair social adjustment; the patient is working well, raising chickens by himself, is still seclusive, hints and suggests in a mysterious way the presence of imaginary ideas—the Masons are responsible for his trouble in some way; he took a Masonic ring to a jeweler and had a cross put on it; he probably has hallucinations; he has persecutory delusions	36
H. H.	Still in the hospital; refuses certain foods and has delusions concerning them	45
C. W.	Subsequent observation suggests that this case is one of cerebral syphilis	?

SUMMARY

These observations are offered as an aid in determining the prognosis in cases of dementia praecox.

Approximately one third of all patients with dementia praecox admitted for the first time during 1932 and 1933 showed some change in the spinal fluid.

Prognosis was bad in this third of the patients.

423 Citizen's Bank Building.

Abstracts from Current Literature

Physiology and Biochemistry

THE ROLE OF CERVICAL NERVES IN FACIAL SENSATIONS AND THE QUANTITATIVE DISTURBANCE OF SENSITIVITY IN MAJOR TRIGEMINAL NEURALGIA. F. H. LEWY, Am. J. M. Sc. **196**:564 (Oct.) 1938.

This study was based on 50 patients suffering from major trigeminal neuralgia. They were examined both before and after subtotal resection of the trigeminal sensory root with von Frey's graduated hairs and thorns and Head's algesimeter. Threshold (513 determinations) and excitation time (929 determinations) with electrical stimulation were determined both for touch and for short pain sensations. Ten normal persons served as additional controls. Frequency curves, in which the threshold values for the touch points, expressed in volts, were plotted against the number of incidences, show two maxima, the one at 15 volts the other at 40 volts. After section of the fifth nerve root, the maximum at 15 volts disappeared, while the maximum at 40 volts remained unchanged. Frequency curves for the time factor of touch sensations showed a similar two-humped curve. After subtotal retrogasserian neurotomy, the figures at 0.2 millisecond disappeared; the values around 0.4 millisecond remained, and a new maximum appeared at 0.6 millisecond. There was a marked difference in the behavior of touch and that of pain sensation over the face after the operation. Not more than 25 per cent of the patients showed complete loss of sensation, but 77 per cent showed a loss of pain sensation in the second and third divisions. The touch points having a low mechanical and electrical threshold and a low time factor are innervated by the fifth nerve; those having high values are supplied by the cervical segments, while the pain points are supplied by the fifth nerve only. The disturbance of sensibility after subtotal section of the fifth nerve root is characterized by complete disappearance of some pain points. The points that remain show a high threshold hypalgesia.

MICHAELS, Boston.

TRANSMISSION OF EXCITATION BETWEEN EXCISED NON-MYELINATED NERVES. H. H. JASPER and A. M. MONNIER, J. Cell. & Comp. Physiol. **11**:259 (April 20) 1938.

According to the classic concept of the transmission of the nerve impulse across a synapse, the action potential from one axon should be capable of exciting another if the axons are placed sufficiently close together for the electrical changes produced by the first axon to reach threshold at the seat of excitation for the second. This problem was tested by studying the nature of the transmission of excitatory effects between adjacent excised crustacean nerve fibers in a juxtaposed nerve preparation. Only a fraction of the fibers in the second nerve were activated by maximal activation of the adjacent first nerve, even in the best preparations, and transmission failed entirely in some instances. It appears that a close contact may be necessary to permit the actual excitation of one fiber by the impulse in an adjacent fiber.

CHORNYAK, Pittsburgh.

THE INFLUENCE OF PHOTODYNAMIC SENSITIZATION ON THE ELECTRICAL AND CHEMICAL STIMULATION OF MUSCLE AND CUTANEOUS NERVE ENDINGS IN THE FROG. ABRAHAM J. KOSMAN, J. Cell. & Comp. Physiol. **11**:279 (April 20) 1938.

This report deals with factors in photodynamic stimulation of skeletal muscle. Previous exposure of the stained muscle to light produces an increased irritability

of the muscle to stimulation with salts and to mechanical and contact influence. The present experiments were devised to determine whether the increased irritability of the muscle is specific to stimulation with salts or whether there is a generally increased irritability to all forms of stimulation. In the experiments reported here the most effective stimulating agents for the photosensitized muscle were pure solutions of sodium salts of the lyotropic series, and the least effective, electrical stimulation.

CHORNYAK, Pittsburgh.

QUANTITATIVE STUDIES ON NERVE REGENERATION IN AMPHIBIA: II. FACTORS CONTROLLING NERVE REGENERATION IN REGENERATING LIMBS. RAYMOND LITWILLER, J. Exper. Zoöl. **79**:377 (Nov.) 1938.

Limbs of the Japanese newt, Triturus pyrrhogaster (Boie), and of the axolotl Amblystoma tigrinum (Green) were amputated at their bases and allowed to regenerate. The regenerated limbs were treated with Bielschowsky's silver method or with a modification of the Weigert-Pal method, and counts of the number of nerve fibers were made throughout the length of the limb at intervals of 200 microns. The size of the cross sectional area of the limb at each interval was also determined. The number of myelinated fibers stained by the Weigert-Pal method averaged about 20 per cent less than the total number of fibers stained by the Bielschowsky technic. The number of nerve fibers, first counted at the base of the regenerate, dropped steadily distally throughout the regenerate, the drop bearing a strict relation to the decrease distally in mass of tissue to be innervated. The number of nerve fibers terminating within any arbitrary slice of a regenerate was in direct proportion to the mass of that slice, with a proportionality constant k. This constant equaled the number of nerve fiber branches ending in a unit of tissue mass and declined with increasing age of regeneration, as well as with increasing age of the animals.

WYMAN, Boston.

STIMULATING EFFECT OF BENZEDRINE ON MENTAL ACTIVITY AND MOOD IN PHYSIOLOGIC AND PATHOLOGIC STATES. T. DE LEHOCZKY, J. belge de neurol. et de psychiat. **38**:537 (July) 1938.

De Lehoczky studied the effects of benzedrine on 100 patients. He found that the drug had a stimulating effect on the higher cortical functions in normal as well as in pathologic states and that it caused a seceondary elevation of mood. In normal persons the drug tends to relieve bodily and mental fatigue rather than to elevate the mood. In this respect it is somewhat similar in its action to some of the alkaloids, but there is no tendency toward habit formation, and there are no symptoms of withdrawal. After prolonged use, nervous exhaustion to the point of fatigue is produced by hyperactivity. The drug is effective in treatment of pathologic states, especially light and moderate depressions. Another important effect is rendering of the patient accessible to active psychotherapy. Benzedrine can be used in treatment of all forms of mental disease in which pathologic fatigue and inhibition play important roles, that is, psychoneuroses, the nervous obsessions and drug addiction. The author obtained the best results in cases of psychoses characterized by inhibition and in cases of depersonalization, by making the patients accessible to psychotherapy. The next best results were obtained in cases of narcolepsy and in oculogyric crises. The author had no encouraging results in treatment of the sequelae of encephalitis. He did not observe elevation of blood pressure in any of his cases and was not able to confirm the statement that the drug has a harmful effect on the cardiovascular system.

DE JONG, Ann Arbor, Mich.

ELECTROENCEPHALOGRAPHIC STUDIES ON EPILEPTIC PATIENTS. P. PAGNIEZ, W. LIBERSON and A. PLICHET, Presse méd. **46**:1465 (Oct. 5) 1938.

Pagniez and his associates made studies in 33 cases of diverse forms of epilepsy, in a small number of which the diagnosis of epilepsy was doubtful. The electroencephalograms were made with occipital, frontorolandic, biparietal, bitemporal

and temporofrontal derivations (recording not simultaneous). In the course of these studies the authors observed paroxysmal as well as permanent modifications in the electroencephalogram. They found that the epileptic patients with violent or frequent attacks and those refractory to treatment or with mental changes showed between the attacks electrical waves of abnormal frequency. In the majority of these cases the dominating frequency was between 6 and 7 per second. Nevertheless, of 12 patients with the severe forms of epilepsy there were 2 who escaped to a certain extent this considerable retardation of the alpha waves, the predominating frequency being from 8 to 9 per second. Moreover, all the patients with severe epilepsy (except a patient who had been operated on) showed electroencephalograms of great or average amplitudes (usually above 50 microvolts). The epileptic patients with less violent and less frequent attacks and those who were benefited by treatment did not show abnormal waves except during the attacks. Some of these patients, moreover, presented electroencephalograms of small amplitude. Thus the electroencephalograms of epileptic patients seem to be an objective indication of the severity of their disorder. This method of examination has not only diagnostic but prognostic value. Moreover, it can be used for medicolegal purposes in the selection of persons for professions and for military service and in control of therapeutic measures. EDITOR'S ABSTRACT.

THE EPITHALAMOEPIPHYSIAL COMPLEX. G. ROUSSY and M. MOSINGER, Rev. neurol. **69**:459, 1938.

Melanin is observed outside the cells of the epiphysis. In the horse it occurs also within the pineal cells and within ramified melanocytes which penetrate between the pineal cells and come in contact with the perivascular nerve fibers and the fibers which come from the habenular region. This represents both hemocrine and neurocrine secretion by the pineal gland, analogous to the pigmentary neurocrinia of the hypophysis. Pigment is sometimes observed in the ependyma of the pineal recess, suggesting that pineal hydrencephalocrinia takes place. Transverse and sagittal serial sections of the dog's brain, stained with silver, show eight nerve fiber tracts leading to the pineal gland: (1) from the taenia thalami of the same side or, via the habenular commissure, from the opposite side; (2) from the posterior commissure through the inferior peduncle of the pineal gland, probably originating in the mesencephalic periventricular system; (3) from the habenular nuclei, ipsilateral and contralateral, via the taenia thalami and the habenular commissure; (4) from the habenular commissure, which, in addition to the tracts already mentioned and the interepithalamic fibers, contains fibers that pass over the dorsal aspect of the pineal gland and end in the tela choroidea and choroid plexus (in keeping with the opinion of Greving); (5) from the periventricular gray matter of the thalamus, via the inferior peduncle of the pineal gland; (6) from the periventricular gray matter of the fourth ventricle, particularly the superior cerebellar peduncle, the gray matter about the iter and the cells in the stratum zonale of the quadrigeminal bodies—all via the stratum zonale itself to the infrapineal zone; (7) from the carotid plexus, called the cervical contingent because it arises from the superior cervical sympathetic ganglion, and (8) from the valvula of Vieussens, which in the dog constitutes a supratectal recess of the fourth ventricle, to the tela choroidea, the veins of Galen and their branches and along some of these veins to the pineal gland.

The tenial contingent connects the epiphysis with the hypothalamus (preoptic zone, tangential nucleus, accessory tangential nucleus) and with the parolfactory zone and innominate substance of Reichert. Thus, the pineal gland receives impulses not only from all the general and special sensory apparatus but also from the subependymal and choroidal receptors and the hypothalamus. The epithalamoepiphysial and the hypothalamohypophysial complexes are functionally correlated both by neural connections and by reciprocal hormonal effects on one another. The latter may be direct (hydrencephalocrinia) or indirect (neurocrinia). A further analogy is drawn between the hypophysis, which developed phylogenetically in contact with the saccus vasculosus, and the epiphysis, which developed in

contact with another sense organ, the pineal eye. In like manner, the subcommissural organ and the carotid sinus can both be regarded as combined sensory and glandular organs. The neurovegetative central nervous system develops not only about the sulcus of His but also in contact with all the ependymal formations.

LIBER, New York.

CORTICAL REPRESENTATION OF THE VAGUS NERVE. P. BAILEY, Confinia neurol. **1**:347, 1938.

By the oscillographic method it was shown that afferent impulses from the vagus nerve reach the cerebral cortex on the under surface of the frontal lobes, the greatest effect being on the contralateral side.

DE JONG, Ann Arbor, Mich.

SPECIFIC DYNAMIC EFFECT OF PROTEINS AFTER PARALYSIS OF THE ORTHOSYMPATHETIC SYSTEM. G. ROTHSCHILD, Arch. f. d. ges. Physiol. **239**:772, 1938.

Rothschild studied the increase in oxygen consumption in cats after intake of proteins. The orthosympathetic system was paralyzed by piperidin methyl-3-benzodioxane ("933 Ff"). The dose administered intraperitoneally was 0.7 cc. of a 1 per cent solution per kilogram of body weight. The experiments were performed with the animal under dial anesthesia, which prevented the marked changes in the metabolism produced by the drug itself in waking animals, without diminishing the specific dynamic effect of proteins. It was found that paralysis of the orthosympathetic system by the drug prevented the increase of gas metabolism that was otherwise induced by ingestion of proteins, indicating that the autonomic system plays an important part in this mechanism.

SPIEGEL, Philadelphia.

RELATIVE COORDINATION IN MAMMALS AND IN MAN. E. VON HOLST, Arch. f. d. ges. Physiol. **240**:44, 1938.

Previous experiments of von Holst have shown that various independent rhythms of locomotor innervations may exist in different parts of the spinal cord of fishes. One rhythm may influence another ("magnet effect"); this may induce equality of both rhythms (absolute coordination) or periodic increase and decrease of the influenced rhythm (relative coordination). Relative coordination may be observed in dogs and in rare cases in horses. The forelegs show a higher locomotor rhythm than the hindlegs. Usually both rhythms vary in such a way that the rhythm of the forelegs increases while that of the hindlegs decreases and vice versa. More rarely, the rhythm of the hindlegs (forelegs) remains constant while that of the forelegs periodically increases (decreases). Thus, there are similarities to the relative coordination of fishes, indicating the existence of a coordinating "magnet effect." In man voluntary movement of the arms in different independent frequencies is possible, but only a few persons succeed in such an innervation. In the majority of persons who try to move both arms in different rhythms with the eyes closed a mutual influence of the rhythms appears. The resulting patterns show similarities to those observed in the relative coordination of fishes.

SPIEGEL, Philadelphia.

FURTHER STUDIES ON THE SHAPE OF THE CEREBRAL POTENTIAL WAVES. H. ROHRACKER, Arch. f. d. ges. Physiol. **240**:191, 1938.

Berger's alpha waves were recorded with high speed film (940 mm. per second). Rohracker is inclined to believe that these waves may be only the expression of metabolic processes of the ganglion cells and that the irregular beta waves are related to psychophysical processes.

SPIEGEL, Philadelphia.

MECHANICAL NERVE STIMULATION. W. SCHMITZ and W. WIEBE, Arch. f. d. ges. Physiol. **240**:289, 1938.

Frog nerves were stimulated mechanically by the vibrating coil of a loud speaker, and the action currents of the nerves were recorded. The graphs of the action currents corresponded to those obtained on submaximal electric stimulation. The speed of conduction was 2.2 meters per second (sciatic nerve of Rana temporaria, winter animals). At the site of stimulation there appeared, even if the nerve was exhausted and did not react, a negative potential proportional to the pressure. Conversely, on decompression a positive potential was observed. The authors conclude that mechanical stimulation may excite the nerve directly, without intermediary electric phenomena, e. g., by concussion of the membranes.

SPIEGEL, Philadelphia.

COORDINATION OF THE SUCKING CENTER AND THE RESPIRATORY CENTER IN THE HUMAN SUCKLING. A. PEIPER, Arch. f. d. ges. Physiol. **240**:312, 1938.

Peiper made simultaneous records of respiratory and sucking movements in the human infant. The basic rhythm of the respiratory center in sucklings is slower than that of the sucking center. On intake of food, the sucking movements are first associated with irregular respiration, diminished amplitude of the respiratory movements or even complete inhibition of respiration; eventually, the sucking center forces its rhythm on the respiratory center. Sometimes one observes an after-effect, the respiration continuing in the sucking rhythm after the sucking has ceased.

SPIEGEL, Philadelphia.

Neuropathology

PATHOLOGIC AND IMMUNOLOGIC STUDIES IN POLIOMYELITIS AND THEIR SIGNIFICANCE IN THERAPY AND TREATMENT. M. BRODIE, Am. J. Pub. Health **28**:746 (June) 1938.

Brodie declares that the virus of poliomyelitis in the experimental animal is strictly neurotropic and travels by way of the nerve tracts. Neither the port of entry nor the pathogenesis has been finally determined in man. The study of immunologic data shows: 1. The presence of serum-neutralizing substances or the so-called antibodies and resistance to the disease do not necessarily correlate. However, in the human being there is evidence that the presence of antibodies may be indicative of immunity. 2. Recovery from poliomyelitis does not, as a rule, result in demonstrable antibodies or neutralizing substances. 3. The so-called neutralizing substance can develop only as a result of specific exposure to the virus. 4. There is evidence that more than one strain of virus exists. Neither convalescent serum nor any of the other available therapeutic measures advocated offers any hope for the prevention or limitation of paralysis. The value of active immunity as a preventive is undetermined. Further studies should be withheld until the pathogenesis in man has been worked out. Nasal sprays are effective in protecting the monkey. In the human subject the results are not encouraging and may not be protective.

EDITOR'S ABSTRACT.

DESTRUCTION OF THE GANGLION CELL IN THE INFANT BRAIN. C. R. TUTHILL, Arch. Path. **26**:463 (Aug.) 1938.

Karyorrhexis of the nuclei of ganglion cells was considered by Spielmeyer to be a disturbance accompanying severe change in ganglion cells resulting from cerebral inflammation. The nuclear protoplasm is broken up into many fine granules, seen either within or without the nuclear periphery; the nucleolus remains intact, and the cytoplasm is swollen and tigrolytic. The nuclear fragments finally fade, and the cell disappears.

This change in the ganglion cells has been observed in the brains of 34 infants, from 7 days to 2 years of age. Since the karyorrhexic changes are seen chiefly in the first six months of postnatal life, the immaturity of the ganglion and glia cells appears to be the factor predisposing toward their destruction by the antagonistic forces of growth. However, a variation in the number of disintegrating ganglion cells in the brains of infants of similar age and disease seems to indicate either greater sensitivity in some of the cells or greater severity of the disease. As only single, separated ganglion cells become karyorrhexic, any resulting gliosis is difficult to recognize in older cases. WINKELMAN, Philadelphia.

SOME OBSERVATIONS ON THE DEPTH AND NERVE-CELL CONTENT OF THE SUPRAGRANULAR CORTEX IN NORMAL AND MENTALLY DEFECTIVE PERSONS. R. M. NORMAN, J. Neurol. & Psychiat. **1**:198 (July) 1938.

Norman examined microscopic sections from three cortical areas of the brains of 30 normal persons and of 30 mentally defective persons whose brains exhibited no gross pathologic changes. The cortical areas which he selected were: (1) Bolton's "visuopsychic" area (area O. A. of von Economo), (2) the frontal pole (area F. E. of von Economo) and (3) the supramarginal gyrus (area P. F. of von Economo). Micrometric measurements of the supragranular cortex failed to reveal any significant difference in the mean depth of the cortex between normal and defective persons, thus disproving Bolton's contention that amentia is associated with specific reduction in the supragranular cortex. However, a series of counts of neuron cells made in the middle of this pyramidal cell lamina disclosed two abnormal processes: (*a*) excessive crowding of the nerve cell bodies, leading to an increased cell count and (*b*) undue sparseness, leading to a low cell count. There was greater variability in the average nerve cell content of different sections as well as in the distribution of cells within the same section in the defective than in the normal brains. There was not significant difference between persons with mongolian and defective persons without mongolism with regard to the mean cell content or variability in the distribution of nerve cells. Norman regards the crowding of the nerve cell bodies as a characteristic feature of the defective brain, which is to be interpreted as a sign of inhibited development. On the other hand, the relative deficiency of nerve cells is also observed in normal brains, although it is more frequent in defective brains. The sparseness of nerve cells may be due either to faulty development or to degenerative phenomena. In general, the investigation supports the view that amentia is commonly associated with structural abnormalities of the parts of the neopallium which have been most recently acquired.

N. MALAMUD, Ann Arbor, Mich.

ULCERS OF THE DIGESTIVE TRACT IN ASSOCIATION WITH CEREBRAL LESIONS. L. OPPER and H. M. ZIMMERMAN, Yale J. Biol. & Med. **11**:49 (Oct.) 1938.

Opper and Zimmerman give the clinical histories and postmortem observations in 22 cases in which ulceration, erosion or malacia of the upper part of the digestive tract (esophagus, stomach or duodenum) was shown. Lesions of varied origin were observed in the brain of each of the 22 patients on whom necropsy was performed. In 1 additional instance the brain was not examined, but the clinical symptoms pointed to organic cerebral involvement. The localization of the lesions was as follows: the nuclei of the interbrain, in 16 instances; the midbrain, in 2 instances, and diffuse cerebral, chiefly cortical, involvement, in 3 instances. In the 3 last cases the diencephalic nuclei were spared. The gastrointestinal lesions in cases of cortical and mesencephalic involvement are probably mediated through the hypothalamic nuclei. Two cases are described in which injury to the diencephalon and mesencephalon was not complicated by lesions in the digestive tract. Such instances emphasize the present lack of knowledge concerning the pathogenesis of lesions of the alimentary tract. AUTHORS' ABSTRACT.

PATHOLOGY OF MÉNIÈRE'S SYNDROME. C. E. HALLPIKE and H. CAIRNS, J. Laryng. & Otol. **53**:625 (Oct.) 1938.

Hallpike and Cairns describe the microscopic changes in the temporal bones of 2 patients with Ménière's syndrome. In each of these the affected temporal bone showed gross distention of the endolymphatic system, together with degenerative changes in the sensory elements. A possible explanation of this distention is suggested by the absence in both patients of the normal area of connective tissue around the saccus endolymphaticus.

EDITOR'S ABSTRACT.

RELATION OF THE DIENCEPHALON TO SOMATIC DEVELOPMENT. MARES CAHANE and TATIANA CAHANE, Rev. franç. d'endocrinol. **16**:181 (June) 1938.

This is an experimental, clinical and pathologic study supporting the theory that the infundibular nuclei participate in the growth mechanism of the body through stimulation of the eosinophilic cells of the hypophysis. Lesions were produced in 10 mice in the region between the optic chiasm and the pituitary stalk. The initial weight of the animals varied from 95 to 158 Gm. At the end of from six to fourteen months the weights varied from 87 to 187 Gm. In a control group the weights varied from 92 to 151 Gm. at the beginning and from 139 to 312 Gm. at the end of observation. The average final weight for the group on which operation was performed was 137 Gm., as compared with 225 Gm. for the control group. Microscopic study revealed rarefaction of the tissue in the anterior lobe of the pituitary. There was a decrease in the number of eosinophilic cells.

The authors report their observations in 3 cases. The first was the case of a youth aged 16 with symptoms of chronic chorea, flaccid paraplegia and infantilism. Necropsy revealed evidence of an inflammatory lesion in the optostriate nuclei and the infundibular region. The hypophysis showed no evidence of inflammation, but there was pronounced rarefaction of the glandular tissue and decrease in the eosinophilic cells. The authors believe that the changes in the hypophysis were responsible for the infantilism, but they regard these changes as secondary to the inflammatory lesion in the optostriate nuclei. The second case was that of a youth aged 18 with the physical development of a child of 13. His father was an alcohol addict. The boy had an attack of "typhoid" in early infancy, was retarded intellectually and had made poor progress in school. His height was 143 cm. and his weight 38 Kg. There was no growth of hair on the face; the secondary sex characteristics were absent; there was enophthalmia, and dentition was not complete. Roentgenograms showed incomplete ossification. The authors regard the condition in this case as a sequel of encephalitis, in which the infundibular region was probably involved. The last case was that of a woman aged 22 with athetosis, infantilism and idiocy. Her height was 133 cm. and her weight 35 Kg. She was said to have had an attack of typhoid. She had never menstruated. The authors think that in this case there was an inflammatory lesion in the diencephalon with secondary involvement of the hypophysis.

NOTKIN, Poughkeepsie, N. Y.

JUVENILE AMAUROTIC IDIOCY. G. MARINESCO, Rev. neurol. **69**:449, 1938.

Marinesco takes issue with Dide and van Bogaert (*Rev. neurol.* **69**:1, 1938) concerning the classification of a case of Marinesco's, cited by these workers as an instance of the late infantile (Dollinger-Bielschowsky) type of amaurotic idiocy. This case should be classified under the juvenile (Spielmeyer-Vogt) type of the disease. The safranophilic granulations described by Dide and van Bogaert were the same as those observed by Marinesco many years earlier and termed by him oxyneutrophilic granulations, apparently a form of mitochondria. Likewise, according to Olmer, in a report made at a meeting of the Réunion biologique de Marseille, Dec. 16, 1902, the granules which occur only in the locus caeruleus were none other than those described by Marinesco in the spinal and sympathetic ganglia. The fuchsinophilic granules (mitochondria?) in nerve cells give rise to

melanin in certain vegetative neurons and to lipofuscin in certain somatic neurons. The physicochemical changes which characterize amaurotic family idiocy are proteolysis, increased osmotic tension, changes in the mitochondria and oxidase granules and variations in the p_H—all phenomena related to autolysis (paper read at a meeting of the Société médicale de Bucarest, June 9, 1920). Schaffer's hypothesis that the primary anomaly associated with amaurotic idiocy is in the hyaloplasm is rejected. The first changes are in the mitochondria.

LIBER, New York.

GENERALIZED POLYRADICULOGANGLIONEURITIS. T. FRACASSI, D. E. GARCIA and A. CASTAÑE DECOUD, Rev. argent. de neurol. **3**:5, 1938.

The authors report 14 cases in which the condition came under the general heading of polyneuronitis. In 3 of the 14 cases the patient died, and autopsy was performed. Pathologic changes were most marked in the spinal ganglia and roots and in the peripheral nerves and were both inflammatory and degenerative in nature. Mild degenerative alterations were seen in the anterior horn cells. Nosologically, this condition, according to the authors, should be grouped with the neuritis of herpes zoster rather than with poliomyelitis or leukoencephalomyelitis.

KING, Princeton, N. J.

LATE FORMS OF AMAUROTIC IDIOCY SHOWING THE PICTURE OF PARALYSIS AGITANS. J. HALLERVORDEN, Monatschr. f. Psychiat. u. Neurol. **99**:74 (April) 1938.

Late forms of amaurotic idiocy with varying clinical pictures have been described by a number of authors. In some instances the illness was preceded by earlier disturbances, such as mental deficiency; these cases are probably to be regarded as examples of late infantile or juvenile amaurotic idiocy with a protracted course and not as genuine examples of the late form of the disorder. However, a sharp separation between the two groups cannot be made. Hallervorden reports the case of a patient who had always been mentally deficient. At the age of 39 he was admitted to a hospital for mental diseases because of increasing mental disturbances. He showed a spastic gait, ataxic phenomena and dysarthria. Finally, there developed the neurologic picture of paralysis agitans, and the patient died, at the age of 54. The brain displayed distinct atrophy. Microscopic examination disclosed an abundance of large, balloon-like nerve cells, which contained lipoid droplets and were typical of amaurotic idiocy. They were observed throughout the brain, but were most numerous in the corpus striatum, hypothalamus, thalamus and substantia nigra. Most of the Purkinje cells of the cerebellum had disappeared. In addition to these characteristic alterations, nerve cells exhibiting neurofibrillar lesions of the Alzheimer type were seen in the cornu ammonis, hypothalamus, thalamus and corpus striatum. Changes of this type, hitherto undescribed in cases of amaurotic idiocy, are not considered specific for senility; they are probably expressions of a particular kind of colloidal alteration of the nerve tissue, but their significance in the present case is obscure.

ROTHSCHILD, Foxborough, Mass.

PATHOLOGIC FEATURES AND PATHOGENESIS OF STURGE-WEBER DISEASE, WITH COMMENTS ON THE HISTOGENESIS OF ANGIOGLIOMA. I. SCHEINKER, Ztschr. f. d. ges. Neurol. u. Psychiat. **163**:604 (Oct.) 1938.

Sturge, an English ophthalmologist, described in 1879 a case of congenital glaucoma, nevus of the face and convulsive attacks. In 1923, Parkes Weber showed that a condition of this type can be diagnosed during life by means of characteristic roentgenographic findings. Scheinker reported the case of a woman aged 54 who was admitted to the hospital with a history of convulsive attacks for five years. The seizures were rarely jacksonian in character. The patient had shown significant mental changes for three years characterized by confabula-

tion, Witzelsucht, forgetfulness and sexual erethism. For a short time before admission she complained of severe headaches and vomiting. There was occasional urinary urgency. Objective examination showed tenderness in the right fronto-parietal region on percussion; exophthalmos, more marked on the right side; horizontal-rotatory nystagmus on looking to the right; right hyposmia; mild left hemiparesis, and a tendency to fall to the left on closing the eyes. The Wassermann reaction of the blood was negative. Early papilledema, more definite on the right side, was present. A roentgenogram of the skull showed a group of small calcifications in the right frontal region. Arrangement of these calcific spots in parallel lines suggested their association with the walls of blood vessels. The patient was operated on during March 1931. The brain was exposed frontotemporally, and a piece of tumor tissue was removed. The patient recovered from the operation. She died suddenly a few years later, during status epilepticus. Autopsy showed a cystic tumor filling almost the entire right frontal lobe. Histologic examination revealed an astrocytoma. In the periphery of the tumor markedly tortuous vessels were noted in the pia, suggesting an angioma. Calcific deposits were noted in the pial vessels and in the capillaries of the superficial layers of the underlying cortex. Similar calcific deposits were observed lying free in the parenchyma and even in some of the ganglion cells. This was especially marked in the deeper layers of the cortex. Chemical study of this substance revealed that it was pseudocalcium.

The tumor formation therefore had two parts—a large glial and a small angiomatous area. The gliogenous tissue in this case cannot be considered merely as a gliosis in reaction to the existence of the angiomatous malformation. Not only was the astrocytoma much larger than the vascular tissues, but the two portions were separated by an area of relatively normal neural parenchyma. The author believes that this is a case of true angioglioma. The explanation lies in the concomitant maldevelopment of ectodermal and mesodermal structures. The astrocytoma developed on the basis of a defective anlage. SAVITSKY, New York.

Meninges and Blood Vessels

CHRONIC SUBDURAL HEMATOMA IN A CHILD. ABRAHAM KAPLAN, Am. J. Dis. Child. **55**:1034 (May) 1938.

Kaplan reports a case of chronic subdural hematoma in a child aged 8 years who began to have frontal headache and occasional attacks of vomiting six weeks after an injury. Three days before examination he complained of diplopia, and internal strabismus developed. Examination revealed dilated pupils, bilateral papilledema, bilateral palsy of the external rectus muscle, slight inconstant nystagmus, weakness of the right side of the face and generalized hypotonia. The deep reflexes were sluggish and the Babinski sign was positive on the right. A chronic subdural hematoma was observed at operation and the patient was discharged a month later with palsy of the left external rectus muscle as the only residual manifestation. This, too, disappeared later.

WAGGONER, Ann Arbor, Mich.

UNIDENTIFIED VIRUS PRODUCING ACUTE MENINGITIS AND PNEUMONITIS IN EXPERIMENTAL ANIMALS. T. FRANCIS JR. and T. P. MAGILL, J. Exper. Med. **68**:147 (Aug.) 1938.

Francis and Magill describe an infectious agent which apparently belongs to the class of filtrable viruses but which, on the basis of the evidence at hand, is not identical with any previously known virus. The virus was repeatedly recovered in 1936 from ferrets inoculated with washings from the throats of patients suffering from an epidemic disease clinically indistinguishable from epidemic influenza. It is impossible, however, to conclude whether the virus is of ferret or of human origin. The virus has multiple tropisms and is pathogenic for mice and ferrets

and for both Macacus rhesus and Macacus cynomolgos monkeys. Intranasal infection of mice and ferrets causes extensive pneumonic lesions of fatal severity. Intracerebral inoculation of the virus produces in monkeys lymphocytic choriomeningitis from which the animal recovers, while in mice rapidly fatal choriomeningitis is produced. Fatal paralysis occurs in a moderate proportion of mice which receive the virus by the intraperitoneal or the subcutaneous route, while the rest become immune to the intracerebral but not to the intranasal test. Subcutaneous inoculation of mice, monkeys, ferrets, rabbits and guinea pigs causes local granulomatous induration of the skin with enlargement of the regional lymph nodes. Although the new agent possesses many features in common with the virus of lymphocytic choriomeningitis and the virus of venereal lymphogranuloma, cross immunity tests have failed to yield any evidence that it is immunologically related to either the virus of venereal lymphogranuloma or the virus of lymphocytic choriomeningitis. For purposes of identification, the name virus of acute meningopneumonitis is suggested.

J. A. M. A.

Spontaneous Subarachnoid Hemorrhage in Children. H. G. Miller, Arch. Dis. Childhood. **13**:258 (Sept.) 1938.

Five cases of spontaneous subarachnoid hemorrhage are reported. Although necropsy was not performed in either of the 2 cases in which the outcome was fatal, Miller states that the diagnosis in every instance was confirmed by examination of the cerebrospinal fluid. The clinical pictures in all 5 cases were so strikingly similar to that known to occur in adults that in the 3 cases in which there were no complicating factors similar pathologic changes are suspected. Intracranial aneurysm of the type that gives rise to subarachnoid hemorrhage in the healthy young adult has not been recorded frequently in children, but if, as structural evidence suggests, those aneurysms are truly congenital, they must be present (perhaps on occasion only) at birth. The frequently reported association between intracranial aneurysm and coarctation of the aorta is further evidence in favor of a congenital origin, and Fearnsides reported a significant case of a definite aneurysm of the circle of Willis observed at necropsy in a child aged 19 months who died of bronchopneumonia complicating gastritis. It is suggested that in 3 of the cases the hemorrhage was in all probability due to rupture of a congenital intracranial aneurysm and that pathologically, as well as clinically, these cases are analogous to those of spontaneous subarachnoid hemorrhage occurring in adults. One of the other 2 patients was at stool when the hemorrhage, with loss of consciousness, occurred. The other pateint had a facial hemangioma, and a similar intracranial pathologic change is suspected as the cause of the hemorrhage. The pyrexial phenomena associated with the hemorrhage were somewhat inconstant as compared with those occurring in adults.

Editor's Abstract.

Meningo-Encephalitis and Orchitis as the Only Symptoms of Mumps. Wilfred Harris and Hugh Bethell, Lancet **2**:422 (Aug. 20) 1938.

It is generally known that meningeal symptoms may be encountered in mumps or epidemic parotitis. The authors emphasize the fact that parotitis is merely a common complication of mumps, and not its essential feature. The cases of 2 male patients aged 17 and 27, respectively, are reported, in which alternating orchitis gave the clue to the diagnosis. In these cases the disease was preceded by severe meningeal symptoms and signs. Sudden severe headache, stiffness of the neck, vomiting, drowsiness, delirium and hyperpyrexia were noted in each instance. The spinal fluid pressure in the younger patient was 170 mm. of water; the fluid was clear and colorless; each cubic millimeter contained 740 leukocytes, 55 per cent of which were lymphocytes, and the chloride content was 690 mg. per hundred cubic centimeters. Both patients recovered, but whether testicular atrophy followed is not known.

Krinsky, Boston.

SEROUS MENINGITIS ASSOCIATED WITH PFEIFFER'S GLANDULAR FEVER. W. HUBER, Schweiz. med. Wchnschr. **68**:892 (July 23) 1938.

Huber says that the combination of Pfeiffer's glandular fever and meningeal symptoms cannot be regarded as rare, for of 10 patients with glandular fever observed at his clinic 3 had noticeable meningism. In 2 of these 3 cases lumbar puncture disclosed pathologic aspects of the cerebrospinal fluid of a nature indicating lymphocytic meningism. In the third case the cell count of the cerebrospinal fluid was at the limit of normality, but there were no other changes. Five other patients with glandular fever, but without signs of meningism, were subjected to spinal puncture; in 3 of these the pressure of the cerebrospinal fluid was increased; in 2 the cell count was increased, and in 2 pathologic protein curves were detected. These changes in the cerebrospinal fluid without clinical signs of meningitis are of interest because they indicate a high incidence of involvement of the meninges in cases of Pfeiffer's glandular fever. This meningeal involvement is probably due to a great affinity of the still unknown causal agent for the central nervous system.

J. A. M. A.

RELATION OF ANOMALIES OF THE CIRCLE OF WILLIS TO ANEURYSM AT THE BASE OF THE BRAIN. A. SLANY, Virchows Arch. f. path. Anat. **301**:62, 1938.

Brief summaries are presented of 26 cases of aneurysm of the circle of Willis that led to fatal intracranial hemorrhage. Necropsies had been performed in Priesel's institute, Vienna, during the preceding ten years. In 14 cases the aneurysm was associated with an anomaly of the vascular circle. The frequency of the association suggests that there may be a causal relation between anomaly and aneurysm of the circle of Willis.

SCHULTZ, Evanston, Ill. [ARCH. PATH.]

MENINGOCOCCIC MENINGITIS TREATED WITH SULFANILAMIDE. A. ELDAHL, Ugesk. f. læger **100**:365 (April 7) 1938.

Eldahl reports 12 cases of serious meningococcic meningitis in children ranging in age from 4 months to 4 years, treated at the Blegdam Hospital with intraspinal and intramuscular injections of a 0.8 per cent solution of sulfanilamide. Intraspinal injections of from 5 to 30 cc. were given daily, the amount in each case being somewhat less than the quantity of spinal fluid removed. Intramuscularly from 35 to 150 cc. was injected daily, the amount depending on the patient's weight. Three patients, or 25 per cent, died; in the preceding six years the average mortality from meningococcic meningitis at the Blegdam Hospital for children under 4 years was 70 per cent. The 9 cases in which recovery occurred included 3 of meningococcic sepsis in which the prognosis was regarded as hopeless on admission.

J. A. M. A.

Diseases of the Brain

NERVOUS COMPLICATIONS OF MEASLES. A. C. E. COLE, Brit. M. J. **1**:1361 (June 25) 1938.

Cole points out that the pathologic changes accompanying nervous complications of measles appear to be identical with those occurring in postvaccinal encephalitis and in the forms of encephalitis following other acute fevers (mumps and chickenpox). A case of the postfebrile variety of measles encephalitis is presented. There was no rash. The encephalitis occurred in a mother of two children after mild attacks of measles in the children. The condition began with multiple focal and diffuse lesions and later involved chiefly the cerebellar functions. The sequelae were minimal, affecting only cerebellar function, and were not accompanied by mental defects or personality changes. The possible diagnosis of acute dis-

seminated sclerosis was excluded by the mental symptoms in the acute attack and by the absence of any further development in over a year. Whether the illness followed an atypical attack of measles without the rash can be less certainly stated.

J. A. M. A.

PARASITIC EPILEPSY. P. PAGNIEZ and A. PLICHET, Presse méd. **46**:937 (June 15) 1938.

Pagniez and Plichet state that they demonstrated in guinea pigs the essential part played by certain cutaneous parasites in the production of epileptic attacks. Further, they review reports from the veterinary literature on the parasitic origin of epileptic attacks in animals. Among others, they cite a disorder known as contagious epilepsy, in hunting dogs, which was found to be caused by otoacariasis. After the destruction of the acari by parasiticides the epileptic attacks of the dog disappeared. Otoacariasis has been reported to elicit epileptic crises also in cats and foxes. In horses epileptic attacks have been known to be produced by the accumulation in the auditory meatus not only of acari but also of Aspergillus niger. That parasitic epilepsy is not limited to mammals is proved by the fact that it has been observed in chickens. Moreover, it seems that intestinal parasites are the causal factor of epilepsy in animals even more often than are the cutaneous parasites. Further, the authors give their attention to the part played by parasites in the pathogenesis of human epilepsy. They are skeptical about a causal connection between parasitism and epilepsy in human subjects and point out that the literature on this problem is obscure. Their personal observations corroborated their skepticism. They report the clinical histories of several epileptic patients infested with parasites, such as Taenia, Oxyuris, Lamblia, Amoeba and Trichomonas. The histories indicate that the expulsion of the parasites exerted no influence on the epilepsy. Thus, the authors arrive at an entirely different conclusion than that which was suggested by the experiments on animals and by the observations in veterinary pathology. On the basis of their clinical observations they conclude that if parasitic epilepsy exists at all in human subjects it is exceptional.

J. A. M. A.

COMPARISON OF FAMILY HISTORIES OF PERSONS WITH TRAUMATIC AND THOSE WITH HEREDITARY EPILEPSY. K. TRÖGER, Ztschr. f. d. ges. Neurol. u. Psychiat. **161**:351 (March) 1938.

From 15,000 cases of epilepsy Tröger selected 100 cases of unquestionable traumatic origin and 100 cases in which at least one sibling also had convulsions. Genealogic studies could be completed in only 29 cases of traumatic type and 31 cases of the hereditary form. Only cases were chosen in which the first attack came between the eighth and the thirty-fifth year. Patients who showed signs of mental deficiency, mental changes or psychopathic tendencies before the injury were excluded from the series. The only cases of nontraumatic origin chosen were those in which there had been attacks for a number of years. In the families of the 31 patients with the hereditary type Tröger found 41 persons with convulsions, and in the families of the 29 patients with the traumatic type he found 11 with attacks. In the material used as a control (relatives of the wives and husbands of the epileptic patients studied), there were 8 cases of definite hereditary epilepsy. In this control series there were 9 probable and 11 questionable cases of epilepsy. Among the relatives of the patients with traumatic epilepsy there were 4 cases of hereditary epilepsy, 1 case in which the disease was probably hereditary, 2 in which it was exogenous, 1 in which it was questionably exogenous and 3 in which it was questionable. In none of the relatives of the patients with the traumatic form were there petit mal seizures. Tröger notes a significantly greater frequency of atypical fainting and attacks of dizziness in relatives of patients with the hereditary type. There was no greater frequency of mental deficiency in the

relatives of this group. Tröger also noted a high frequency of migraine in uncles and cousins of patients with the hereditary type, a greater number of sinistrals among nephews and nieces in the same group and a relative increase in the incidence of convulsions in childhood in uncles and cousins in the group used for control. There were no greater number of persons with psychopathic personalities and character disorders among relatives of patients with the hereditary type than among those of persons with traumatic epilepsy or in the control material.

This study indicates that, as a rule, genetic factors play no role in the appearance of convulsive disorders following trauma to the head. In an occasional case study of the family history may indicate that such a predisposition is a contributory factor.

SAVITSKY, New York.

OTOGENOUS ENCEPHALITIS PURULENTA PROGRESSIVA. HANS BRUNER and ROBERT DINOLT, Ztschr. f. d. ges. Neurol. u. Psychiat. **162**:106 (March) 1938.

Bruner and Dinolt report 2 cases of diffuse hemorrhagic purulent encephalitis following infection of the ear in men aged 44 and 34, respectively. In both cases the disease followed an acute exacerbation of chronic otitis media. In the first case there was extension of the infection from a thrombosed sinus to the occipital lobe, and in the other direct extension from the infected ear along the pial vessels into the contiguous temporal lobe. In neither case was an abscess observed at necropsy, though in the first case the duration of the illness was ten and in the second twenty-three days. Focal signs of involvement were present. In both instances a clinical diagnosis of abscess of the brain was made, though exploration gave normal results. The authors suggest the term otogenous encephalitis phlegmonosa for this condition, especially because of the rapid spread of the purulent infection. Microscopic examination showed considerable polymorphonuclear infiltration but no abscess formation which could be treated surgically.

SAVITSKY, New York.

APOPLECTIFORM ONSET (HEMIPLEGIA) IN CASES OF TUMORS OF THE BRAIN. A. STENDER, Ztschr. f. d. ges. Neurol. u. Psychiat. **163**:123 (July) 1938.

Stender reports 12 cases of verified tumors of the brain in which there was an acute onset with hemiplegia. They included 5 cases of glioblastoma multiforme, 2 of hemangioma, 3 of astrocytoma or spongioblastoma polare, 1 of a metastatic tumor and 1 of a meningioma in the region of the frontal pole. In most of the cases there were no significant prodromal symptoms; if present they were not marked and not severe enough to interfere with the patient's usual activities. In 6 cases there was headache, and in 2 mental changes were noted. In 5 cases the onset was apoplectiform. In 5 cases there was no evidence of papilledema; in 2 there were dilatation of veins and blurring of the edges of the disks. In 2 cases there was definite papilledema, and in 4, marked elevation of the optic disks. In 1 case there was spasticity, the patient having been examined a relatively long time after the ictus. Superficial sensory changes were found in 6 cases and deep sensory changes in 2. There were complete aphasia in 2 cases, and definite hemianopia in 2. In 5 cases the tumor was in the frontal region, and in 2, in the posterior part of the subcortex of the frontal lobes with extension into the corpus callosum. In 1 case there was involvement of the basal ganglia only, and in 1, of the corpus callosum. In 2 cases the temporal lobe was involved, and in 1 case the white substance of the whole hemisphere was infiltrated.

In both cases of hemangioma there was a large intracerebral hemorrhage, which explained the sudden onset of the hemiplegia. In some of the other cases there were small hemorrhages and extensive necrotic areas, insufficient to explain the sudden hemiplegia. In no case could it be shown that the sudden hemiplegia was due to the occlusion of a large blood vessel by direct pressure of the tumor. It is suggested that reflex spasms of neighboring blood vessels may take place

when a smaller branch is compressed by an expanding tumor. Marked cerebral edema was observed in all 11 cases in which autopsy was performed. In none of the cases was the *Hirnschwellung* of Reichardt noted. Stender believes that the sudden appearance of cerebral edema around the tumor is the most probable explanation of the apoplectiform onset in cases of tumor of the brain.

SAVITSKY, New York.

GUNSHOT WOUNDS OF THE BRAIN. S. T. KWAN and Y. C. CHAO, Chinese M. J. **53**:439 (May) 1938.

Kwan and Chao present the results in 61 cases of gunshot wound of the brain in which treatment was given in the Peiping Union Medical College Hospital during the last fifteen years. The mortality for the total number of cases, in each of which the dura had been penetrated, was 52.8 per cent. Of 38 patients admitted in a fully conscious mental state, 13 died; 10 of 12 patients admitted in a semiconscious state died, and of 11 patients admitted in a totally unconscious condition, 9 died. About 46 per cent of the patients showed some form of widespread paralysis. Of the 26 instances in which cultures of the wound were made, streptococci appeared in 18, staphylococci in 11 and Bacillus coli in 3. Bacteriologic examination of the cerebrospinal fluid is of great importance: Twenty-four patients showed signs of meningeal irritation; 12 of these patients had positive cultures, and all of them died. Operative treatment was given to 39 patients, and of these 16 survived, the operative mortality being 58.9 per cent. The procedures carried out varied, but included drainage of the wound (including the scalp, skull and brain), drainage combined with débridement and drainage of the abscess of the brain. Meningitis was responsible for 12 deaths; gross destruction of cerebral tissue with extensive paralysis of cerebral function, for 11 deaths; bronchopneumonia and Streptococcic bacteremia were each responsible for the death of 3 patients, and 1 death each was attributed to abscess of the brain, abscess of the brain complicated by acute uremia and uremia alone.

J. A. M. A.

TUMORS IN THE POSTERIOR CRANIAL CAVITY. A. TORKILDSEN, Norsk mag. f. lægevidensk. **99**:495 (May) 1938.

Torkildsen analyzes 34 cases (23 of gliomas, 7 of tuberculomas, 1 of meningioma, 1 of cholesteatoma and 2 of tumors of unknown nature established only by ventriculography) occurring in 19 men and 15 women, of whom 18 were less than 20 years old and only 6 more than 40. The average duration of the disease was eighteen months. Of his entire material of 154 cases of verified tumors of the brain (*Norsk mag. f. Lægevidensk.* **99**:137 [Feb.]; 310 [March] 1938) 8 (about 5 per cent) were instances of tuberculoma; the tumor in the eighth case was located in the pons. The most frequent symptom was headache, which occurred in 31 cases and was the first symptom in 25. Vomiting and nausea occurred in 26 cases and were the first symptoms in 10. Dizziness was one of the first three symptoms in 15 cases. There were bilateral choking of the disks in 27 cases and unilateral in 2. Paralysis of the muscles of the eye occurred in 15 cases. Pure motor and sensory symptoms were infrequent. In 8 cases there was paralysis or rigidity of one or more extremities, and in 2 cases general paresis, in one of which it was combined with coarse tremor. One case of astereognosis with tumor in the vermis is described. In the cases in which there were signs of cerebellar dysfunction the duration was about half that in the cases in which there was not such dysfunction. The only certain result of roentgen examination was an expression of increased intracranial pressure. Pathologic increase in albumin in the spinal fluid was established in more than half the cases in which it was determined; the cell count was definitely increased in only 1 instance (tuberculoma). The author's material also includes 16 cases of tumor of the acoustic

nerve, 7 in men and 9 in women, of whom none was less than 20 years old and 10 were more than 40. The average duration was twenty-nine months. The most common symptoms were headache, in 14 cases; unilateral deafness, dizziness, nausea and vomiting, each in 7 cases, and tinnitus, in 5 cases. Nausea and vomiting occurred twice as often with tumors in the posterior fossa as with tumor of the nervus acusticus. Mental disturbances were present in 4 cases, motor disturbances in 4 and hemihypesthesia in 2. In 6 cases destruction of the pyramid together with distention of the porus acusticus internus on the affected side was established roentgenologically. The albumin content of the spinal fluid was increased in the 6 cases in which it was determined; in 4 there was an increased cell count.

J. A. M. A.

Vegetative and Endocrine Systems

ADIPOSITY AND DIABETES MELLITUS IN A MONKEY WITH HYPOTHALAMIC LESIONS. S. W. RANSON, C. FISHER and W. R. INGRAM, Endocrinology **23**:175 (Aug.) 1938.

Ranson, Fisher and Ingram placed lesions in the hypothalamus of 50 monkeys and over 300 cats; in only 1 animal, a monkey, was definitely pathologic adiposity observed. The condition developed within three weeks after the operation. The adiposity was associated with diabetes mellitus and moderate disturbance in the capacity to regulate body temperature. Two months after operation the weight of the monkey had more than doubled, and in six months, more than tripled. The increase in weight was associated with marked polyphagia. The monkey ate constantly and showed great greediness. At autopsy normal mature testes were seen; there was evidence that premature descent of the testes may have occurred. Associated diabetes mellitus was explained by the hydropic degeneration of the islets of Langerhans. The lesions in the hypothalamus were similar to those in a number of other monkeys which showed no tendency to adiposity. Study of the histologic structure of the hypophysis, the adrenal glands and the thyroid yielded no clear evidence concerning the cause of the adiposity. It is worth noting that the animal presented some elements of the syndrome of basophilic adenoma, evidenced by the marked girdle adiposity, hyperglycemia and glycosuria.

PALMER, Philadelphia.

HISTOLOGIC EFFECTS INDUCED IN THE ANTERIOR PITUITARY OF THE RAT BY PROLONGED INJECTION OF ESTRIN WITH PARTICULAR REFERENCE TO THE PRODUCTION OF PITUITARY ADENOMATA. J. M. WOLFE and A. W. WRIGHT, Endocrinology **23**:200 (Aug.) 1938.

Wolfe and Wright made histologic studies of the reaction of the anterior lobe of the hypophysis to injections of estrogen (estradiol benzoate) for periods ranging from thirty days to over a year. Cell counts were made on all the glands studied. The pituitary glands of castrated female rats which received 200 rat units of estrogen daily for eighty days were only slightly heavier than those of rats which received estrogen for thirty days. The reactions obtained in castrated and in noncastrated animals were similar. Nine animals, both males and females, one half of which were castrated, received daily injections of 200 rat units for a period ranging from one hundred and eighty to one hunded and forty-five days. Eight castrated female rats received interrupted injections of estrogen. This procedure was repeated eight times, and the animals were killed on the two hundred and forty-seventh day. In this group of 17 rats two types of cellular reaction in the anterior lobe of the hypophysis were observed. In 8 rats the reaction was generalized, a uniform histologic structure being observed through the whole gland. The pituitary glands showing a generalized reaction were markedly increased in weight, which ranged from 43 to 85 mg. The eosinophilic cells

showed marked degeneration; the basophilic cells had undergone complete degeneration, and the chromophobic cells were markedly increased in number. In 9 animals there were adenomatous glands, some weighing as much as 248 mg. Three types of adenomas were described: pituitary adenomas associated with profound vascular changes, small nodular foci of cells presenting structural characteristics different from those of cells of the surrounding extra-adenomatous tissue and diffuse adenomatous hyperplasia of the entire gland. A vacuolar condition of the cells of the anterior lobe, considered to be degenerative, was present. Mitotic figures were generally more abundant in the rats given injections for shorter periods.

PALMER, Philadelphia.

CELLULAR CHANGES IN THE ANTERIOR HYPOPHYSES OF VITAMIN-A DEFICIENT RATS. T. S. SUTTON and B. J. BRIEF, Endocrinology **23**:211 (Aug.) 1938.

In view of the proved sterility resulting from lack of vitamin A in animal diets, Sutton and Brief made a study of the cytologic changes in the pituitary gland of 24 day old rats who were deprived of vitamin A. After depletion, as indicated by cessation of growth, the diet was supplemented with standard reference cod liver oil, varying in amount from 1 to 1.4 U. S. P. XI vitamin A units per day. The period between weaning and depletion was from five to six weeks, and the diet supplemented with vitamin A was maintained for approximately seven weeks. At the end of from the one hundred and eighth to the one hundred and twelfth day, the rats showed an extreme degree of vitamin A deficiency, evidenced by loss of weight, xerophthalmia, muscular incoordination and respiratory disorders. On histologic examination there was a significant increase in the "basophilic" cells in animals of both sexes. This increase was greatest in the males and approached the condition seen in true castrated animals. The greater increase in the male may be accounted for on the basis of more nearly complete destruction of the germinal epithelium of the male gonad. The study presents further evidence that the diet deficient in vitamin A causes direct damage to the gonad and the increase of beta cells represents a compensatory change in the hypophysis.

PALMER, Philadelphia.

Treatment, Neurosurgery

CONVULSIVE SHOCK THERAPY IN DEPRESSIVE PSYCHOSES. A. E. BENNETT, Am. J. M. Sc. **196**:420 (Sept.) 1938.

Attempts to relieve depressive psychoses with insulin shock therapy have been discouraging. Therefore metrazol (pentamethylenetetrazol) shock therapy was resorted to in 10 patients with depressive psychoses. In all the cases the psychosis was essentially of the affective type; in none were there schizophrenic features; in 4 there were severe types of involuntional melancholia. Intravenous injections of from 3 to 12 cc. of metrazol were given every two or three days for an average course of five convulsive shocks. Uniformly excellent results were obtained in all cases. The depressive features cleared within two weeks after treatment was begun. The profound temporary change in cerebral circulation resulting from induced convulsions alters physiologically the pathologic anxiety and depressive affective reactions. The result obtained is not entirely psychologic.

MICHAELS, Boston.

DIRECT IMPLANTATION OF FREE NERVE GRAFTS BETWEEN FACIAL MUSCULATURE AND FACIAL TRUNK. EDGAR P. CALDWELL, Arch. Otolaryng. **27**:469 (April) 1938.

Caldwell reports the first case of successful application of a free nerve graft from a facial nerve trunk direct to the facial musculature. In removal of a tumor of the parotid gland it was necessary to divide the trunk of the facial nerve

proximally and all the small peripheral branches as they emerged from the tumor. One week after removal of the tumor the wound was reopened, and the degenerated cutaneous branches of the anterior cutaneous nerves were planted between the freshened end of the stump and the peripheral twigs which could still be identified. They were sutured to the stump and approximated without suture to the twigs. Short tunnels into the muscle planes of the face were dissected, and four fresh branches of the anterior femoral cutaneous nerve were transplanted and laid out in these prepared channels, the proximal ends being sutured to the nerve. The distal ends were spread out in fan fashion in the muscles of the face. Six months later complete facial paralysis was present, but electrical stimulation gave evidence of regeneration. One year later there were good function for both voluntary and emotional response in the lower two thirds of the face and good closure of the eye, but the forehead showed no function.

HUNTER, Philadelphia.

SODIUM DIPHENYL HYDANTOINATE IN TREATMENT OF CONVULSIVE DISORDERS. H. H. MERRITT and T. J. PUTNAM, J. A. M. A. **111**:1068 (Sept. 17) 1938.

In order to determine the relative effectiveness of sodium diphenyl hydantoinate on convulsive disorders in man, Merritt and Putnam selected a group of patients who had had frequent convulsive seizures for many years and had obtained little or no benefit from the usually accepted treatment, i. e., bromides, phenobarbital, ketogenic diet and a restricted fluid intake. The majority of these patients would be classified as having severe epilepsy. The medicament was administered to 200 patients for a period varying from three weeks to eleven months. The results reported in this study are those observed in 142 patients with frequent attacks who received the treatment for a period greater than two months, with extremes of eleven and two months and an average of four and three-tenths months. The dose used for adults varied from 0.2 to 0.6 Gm. a day, depending on the therapeutic effect and toxic reactions. As a rule, for adult patients the dose started with 0.1 Gm. three times a day and was increased to a maximum of 0.2 Gm. three times a day if therapeutic effects were not obtained. For small children the dose started with 0.1 Gm. twice a day and increased to 0.4 or 0.5 Gm. daily until the optimal therapeutic dose was determined. For convenience, the medicament was usually administered at meal time. Gastric symptoms were avoided by having the patient take the drug along with or after, rather than before, the meal. The dose for the 72 patients who were relieved from their attacks varied from 0.2 to 0.6 Gm., with an average of 3.6 Gm. Relief was obtained with a dose of 0.3 Gm. a day by 42 patients. In contrast, the average dose for the 45 patients in whom the attacks were greatly decreased in frequency was 4.3 Gm., and for the unimproved group the average dose was 4.6 Gm. The appearance of minor toxic symptoms, such as nervousness, tremors or ataxia, calls for reduction in the size of the dose. If the reduced dose is ineffective, attempts to increase it can be made after from five to ten days. The use of the drug should be immediately discontinued if more serious toxic symptoms, dermatitis, purpura and the like develop. Exfoliative dermatitis contraindicates further use of the drug. There were no fatalities. Toxic dermatitis occurred in 10 patients, nonthrombocytopenic purpura in 1 patient and minor (in many instances, transient) toxic reactions, tremors, ataxia, dizziness and the like in approximately 15 per cent of the patients. If patients have been receiving large doses of bromides or phenobarbital, these drugs should be continued with the sodium diphenyl hydantoinate, the dose of the bromides or phenobarbital being gradually decreased over a period of from four to seven days. This is advisable since the sudden withdrawal of the bromides or phenobarbital may result in the precipitation of a series of attacks before a reservoir of sodium diphenyl hydantoinate has been built up. The authors' experience with the drug has not been sufficient to determine all the contraindications for its use. At present they believe that it should not be given to elderly persons with hypertension or other evidences of cardiorenal disease or to debilitated patients.

INSULIN IN THE TREATMENT OF ACUTE MANIA. L. C. GROSH, J. Nerv. & Ment. Dis. **87**:559 (May) 1938.

In 2 cases of acute mania Grosh found a tendency toward a decreased tolerance for dextrose during the manic stage and a relatively normal tolerance during the normal stage. Treatment of the manic episodes was therefore instituted with doses of from 10 to 20 units of insulin repeated from four to six times on each of several successive days. Hypoglycemic shock was avoided, and the dose was gradually reduced after three or four days of treatment. In Grosh's opinion, the results of this treatment were seen in the return of the patients to normal activity after about seven days of the regimen, although previous attacks had lasted in the 1 case from four to eight weeks and in the other from five to twenty-five weeks.

MACKAY, Chicago.

PROSTIGMINE IN MYASTHENIA GRAVIS: REPORT OF TWO CASES. M. TARLAU, J. Nerv. & Ment. Dis. **88**:330 (Sept.) 1938.

Tarlau reports 2 cases of myasthenia gravis in which the oral use of prostigmine elicited a remission of symptoms. The remission was temporary in 1 case, with the subsequent death of the patient, and complete for nine months (to the time of writing) in the other. In the patient who died there developed a rapidly increasing tolerance or refractoriness to the drug. This phenomenon was not observed in the other case. Prostigmine was found to be more effective than any other medicament used.

J. A. M. A.

TREATMENT OF PNEUMOCOCCIC MENINGITIS. M. FINLAND, J. W. BROWN and A. E. RAUH, New England J. Med. **218**:1033 (June 23) 1938.

Of 99 patients with pneumococcic meningitis, none recovered except 6 of the 10 whom Finland and his co-workers treated with sulfanilamide alone or with serum. The procedure adopted was as follows: 1. Complete and frequent drainage of the spinal fluid was carried out. 2. Continuous large doses of sulfanilamide by mouth or by subcutaneous injection, if necessary, were used immediately. The optimal dose has not been determined. Sodium bicarbonate was given with each dose. 3. The pneumococcus was identified as rapidly as possible, and sufficient specific antipneumococcus serum was given intravenously to establish a balance of antibody in the circulating blood. 4. Moderate intake of fluid was maintained. 5. About two hours after a reasonable dose was given, blood was withdrawn, and the serum was separated. 6. At the time of the next lumbar puncture this serum was given intraspinally (from 5 to 10 cc.). 7. Lumbar punctures were repeated until the fluid was normal. The frequency was determined by the initial pressure of the fluid and its cellular and protein contents. 8. Transfusions were given after the first week of sulfanilamide therapy if anemia developed and were repeated, as necessary, until the drug was discontinued (after from seven to fourteen days on which the fluid was sterile). These procedures serve to insure a balance of antibody in the blood stream and to control the bacteremia. They should, in most instances in which the sulfanilamide effectively reduces the infection, provide an adequate amount of antibody and complement in optimal proportions and in a medium which is likely to give the least local or general reaction and the greatest antibacterial effect.

J. A. M. A.

EFFECTS OF INTRAMUSCULAR INJECTIONS OF VITAMIN B_1 ON ACUTE LEPROUS NEURITIS AND OF ORAL ADMINISTRATION ON THE GENERAL DISEASE: PRELIMINARY REPORT. L. F. BADGER and D. W. PATRICK, Pub. Health Rep. **53**:969 (June 17) 1938.

During the last six months Badger and Patrick treated 10 patients who had severe acute leprous neuritis of the peripheral nerves with intramuscular injections of thiamin chloride. The injections were begun as soon as possible after the onset

of symptoms, or when the patient first complained of pain. The procedure followed was administration of 300 international units once a day by intramuscular injection and twice a day by mouth. Of the 7 cases in which the injections were begun on the day of onset, the pain disappeared completely twenty-four hours after the first injection in 4, in forty-eight hours in 1 and on the fourth day in another. In 1 case, owing to required emergency treatment, the injections were discontinued after two had been given; on the third day the pain was moderate, after which it continued to lessen in severity until the seventh day, when it was no longer present. Tenderness could no longer be elicited after twenty-four hours in 1 case and after three or four days in all but the 1 case in which the treatment was interrupted. In this case no tenderness could be elicited on the seventh day. In each case the tenderness was less marked twenty-four hours after the first injection. Definite diminution in the swelling occurred about the time that the tenderness disappeared. In 1 case the treatment by injection was begun on the second day of symptoms, and twenty-four hours later the pain lessened definitely. The pain disappeared entirely after three injections, and after four injections the tenderness disappeared completely. In 2 cases the injections were begun on the fourth and fifth days of symptoms. In the former the response to treatment was not as abrupt, and the improvement was not sharply defined from day to day. In the other case the results were about as prompt as in the majority of the cases.

J. A. M. A.

BENZEDRINE IN MENTAL DISEASE. E. W. ANDERSON, Brit. M. J. **2**:60 (July 9) 1938.

Anderson gave benzedrine sulfate orally, in daily doses ranging from 5 to 45 mg., to 33 patients with minor forms of mental disorders and to 8 normal subjects. In the case of 15 patients it was necessary to discontinue the drug because of untoward effects. In 2 others the drug appeared to be of no value and was discontinued. In 11 patients a beneficial effect could be claimed, in some cases with reservations. In 5 no mental, physical or psychic effect was produced. Of the 11 patients who appeared to benefit from the drug, only 3 had no physical symptoms—that is, the drug appeared to exert its effect in the psychic sphere alone. The principal symptoms were headaches, giddiness and cardiovascular symptoms. Of the normal subjects, 1 had decreased and another increased frequency of micturition; 2 had pain in the chest; 1 had palpitation; 1 had anorexia; 1 felt giddy and tired, and 1 had no physical symptoms. The best results with the drug were obtained with the depressed patients. The drug is perhaps of greatest value in the terminal stages of a depression—that is, when clinical improvement has already appeared. With regard to sleep, the results were variable. Of the normal subjects all but 2 experienced an increase in mental or physical activity. It is difficult to claim any great therapeutic value from benzedrine, but its use relieves the depressed patient transiently and gives him a few hours' respite. It should be used cautiously.

J. A. M. A.

PROSPECTS OF SURVIVAL AND CURE IN DEMENTIA PARALYTICA: EIGHTY CATAMNESES TEN YEARS AFTER MALARIAL THERAPY. P. VERVAECK, J. belge de neurol. et de psychiat. **38**:508 (July) 1938.

Vervaeck investigated the condition of patients with dementia paralytica ten years after they had been treated at a psychiatric clinic in Brussels. Investigations were made on the men who had been treated during the years 1926 and 1927. Dementia paralytica being less frequent in women, the follow-up studies were extended to the women who received treatment during the four years from 1925 to 1928, inclusive. Of 50 men, 41 had been subjected to malaria therapy, and of 53 women, 42 had been so treated. Of the 41 men who had been treated with

malaria, 7 were still outside an asylum ten years later, but 1 of these died two months later at the age of 53; 4 others had died outside an asylum, 1 of them after a second sojourn there; 1 lives in an asylum, again demented after having been at liberty for two years; 7 died in an asylum to which they had returned; 7 live in an asylum which they have never been able to leave; 13 died in the asylum, never having left it; 2 disappeared from observation; 1 of these was probably cured. In evaluating these results, the author concludes that in 64 per cent of the men with dementia paralytica who had been subjected to malaria therapy the results were unfavorable. After citing the subsequent fate of the 42 women with dementia paralytica who had received malaria therapy, the author shows that of these the frankly unfavorable results likewise amounted to 64 per cent. J. A. M. A.

Comparison of Treatments (Serum, Rubiazol, Sulfanilamide) of Cerebrospinal Meningitis in Rural Colonial Regions. G. Muraz, H. Chirle and A. Quéguiner, Presse méd. **46**:1113 (July 16) 1938.

Muraz and his associates report their experience in the treatment of cerebrospinal meningitis in epidemics that occurred in French Nigeria. Of 47 patients who were treated with serum, 37 were cured. They report the cases of 4 patients treated with the original prontosil (the hydrochloride of 4-sulfamido-2',4'-diaminoazobenzene) by mouth as well as intramuscularly. Of the 4 patients, 2 were cured. The authors describe their experiences with sulfanilamide administered by mouth or intraspinally. During the first two days as many as 16 tablets (4 four times daily) were given (each tablet containing 0.3 Gm.). During the following six or ten days, about half that dose was administered (2 tablets four times daily). The average number of tablets given to adults in the course of the entire treatment was 100. They emphasize the simplicity of the oral administration of the sulfanilamide preparation and say that this treatment reduced the mortality to 16.39 per cent; that is, the mortality was less than that in serotherapy. They stress that sulfanilamide treatment is much less expensive than serotherapy. The combination of serotherapy with oral sulfanilamide treatment, which was employed by other investigators in 23 cases, resulted in cure in 21 instances.

J. A. M. A.

Acetarsone Therapy of Dementia Paralytica. L. Marchand, Presse méd. **46**:1211 (Aug. 6) 1938.

Marchand's report is based on the results obtained with acetarsone in the treatment of 111 patients with dementia paralytica. None of the patients treated were, or had been, subjected to malaria therapy. Three times a week the patients were given a subcutaneous injection of 1 Gm. of sodium acetarsone dissolved in 1 cc. of distilled water. The total for a series of treatments was 45 Gm. The series were separated by intervals of three or four weeks.

In the case of some of the patients, in whom the dementia paralytica advanced rapidly, the author intercalated between the injections of acetarsone an injection of quinine bismuth iodide until a gingival border appeared.

He tabulates the results of the treatment. He says that he obtained "social recuperation" in 71 (64 per cent) of the 111 patients and improvement in 10 patients (9 per cent); 15 patients (13.5 per cent) died. The author speaks of "social recuperation" in patients in whom the mental defects have disappeared so that they are able to resume their former occupations but who are not cured organically. Social recuperation was obtained in 26 patients after one series of treatments, in 26 after two series, in 11 after three series, in 6 after four series and in 2 after five series. Marchan says that 9 of the patients had to be hospitalized again because of the recurrence of mental disturbances. Relapses are due to premature arrest of the treatment, to insufficient doses or to excessive length

of the intervals between the series of injections. The patients with dementia paralytica who have been treated with acetarsone should be kept under clinical and serologic control for several years after the treatment. The complications that may appear in the treatment with acetarsone are slight as compared with the severity of the disease. The author says that the treatment should be avoided in senile subjects who present organic difficulties. However, tabetic symptoms and alcoholism without hepatic insufficiency do not constitute contraindications to treatment with acetarsone.

J. A. M. A.

TREATMENT OF EPIDEMIC CEREBROSPINAL MENINGITIS WITH SERUM PREPARED WITH STRAINS OF MENINGOCOCCUS FROM CITY OF EPIDEMIC FOCUS. A. NACCARI, Pediatria **46**:509 (June) 1938.

Naccari states that the therapeutic action of antimeningococcus serum depends on the amount of bacteriotropines contained in the serum and on the specificity of the bacteriotropines for a given type of meningococcus. Bacteriotropines are more specific for meningococcus of the type which is used in the preparation of the serum than for other types. The author reports 21 cases of epidemic cerebrospinal meningitis in infants and children. The patients were treated with serum prepared with strains of meningococci which were isolated from patients in the same city. The serum was administered generally through the spinal route and in some cases through the ventricular route. It was given daily in large doses up to 100 to 206 cc., and in rare cases in doses of 380 cc. The treatment lasted from eight to thirty days, and in rare cases forty days. It was discontinued when clear cerebrospinal fluid appeared. Early administration is important. Five of 7 patients whose treatment was started in the course of the first week of the disease recovered. Treatment of the remaining patients in the group began from the tenth to the twentieth day after onset of the disease. In all the cases which ended in recovery the improvement was manifest after the first few injections. Twelve of the patients recovered. The author calls attention to the fact that the percentage of recoveries is twice as great in patients treated with antiserum prepared with local meningococci as in those treated with antiserums prepared with meningococci from other places. He points out the advisability of preparing the antiserum in different cities for local use.

J. A. M. A.

TREATMENT OF EPIDEMIC ENCEPHALITIS BY INTRASPINAL INJECTION OF NORMAL SERUM. T. So, Kitasato Arch. Exper. Med. **15**:101 (April) 1938.

Eleven patients with epidemic encephalitis were treated by So with intraspinal injections of the serum of normal persons. Serums were obtained from four healthy members of the patients' families and three normal men in the laboratory. These serums were not inactivated, nor was a disinfectant added. Serums were never used if they were older than three days. The quantity of serum used was from 3 to 8 cc., and it was introduced slowly into the spinal cavity by lumbar puncture. Before the serum was administered a narcotic was injected, as the injection of the serum occasionally caused temporary stimulating symptoms. The most remarkable thing about the treatment is the prompt lowering of the temperature of the body (for from several hours to twenty-four hours) and the rapid recovery of consciousness. A larger quantity of serum appears to be more effective than a smaller dose, especially in severe forms of the disease. Even in advanced stages the administration of normal serum produces a rapid fall of temperature. There appeared to be no difference in the effectiveness of the serum whether it was taken from blood relatives or from other persons.

J. A. M. A.

Special Senses

ENCEPHALITIC OPTIC NEURITIS AND ATROPHY DUE TO MUMPS. C. M. SWAB, Arch. Ophth. **19**:926 (June) 1938.

Swab reports the case of a man aged 25 in whom meningitis developed after mumps, with normal pressure and chemical constituents of the spinal fluid except for an increase in the protein content. The illness terminated with 3/200 vision in the right eye and 1.5/200 vision in the left and with a high degree of postneuritic bilateral atrophy of the optic nerve.

SPAETH, Philadelphia.

PERIMETRIC STUDIES IN SYPHILITIC OPTIC NEUROPATHIES. L. L. SLOAN and ALAN C. WOODS, Arch. Ophth. **20**:201 (Aug.) 1938.

The cases of this study were subdivided into four general groups: (*a*) cases of clinical primary atrophy of the optic nerve; (*b*) cases of defects in the visual fields associated with normal optic nerves; (*c*) cases of homonymous defects in the visual fields, and (*d*) cases of active or inactive optic neuritis. In the first group of 56 cases the changes in the fields were of four general types; (*a*) concentric contraction of the peripheral field associated with late loss of vision; (*b*) sector-shaped, or nerve bundle, defects, with which loss of vision might be early or late, depending on the involvement of the papillomacular bundle; (*c*) central or cecocentral scotoma with normal peripheral fields, associated with early loss of visual acuity, and (*d*) central or cecocentral scotoma with defects in the peripheral fields, also associated with early loss of vision.

There was a definite relationship between the type of atrophy of the optic nerve and that of the field defect. Special involvement of the papillomacular bundle was noted in many of the cases. Only 2 of the 8 patients with central scotomas and with normal peripheral visual fields showed generalized atrophy of the nerves. A study of the relationship of visual acuity, ophthalmoscopic findings and visual fields in the 56 cases presented suggested that the changes in the visual fields are probably the earliest clinical evidences of atrophy of the optic nerve.

Perimetric examinations were carried out on 200 neurosyphilitic patients whose optic disks were normal or showed only questionable pallor. In 12 patients definite slight defects were found in the visual fields. Of these 12 patients, several were followed for from three months to five years. Since none of these patients has yet shown unquestioned pallor of the disks, definite proof is lacking that the field defects were due to incipient atrophy.

Homonymous defects were found in the visual fields of 12 of 291 patients with syphilis of the central nervous system. These homonymous defects were partial or complete hemanopia, homonymous quadrantic defects, homonymous scotomas and, in 1 case, double quadrantic defects. A study of these 12 cases indicated that the lesions responsible for the visual defects lay posterior to the chiasm and were not definitely related to the syphilitic infection.

There were 23 patients in the group with active or inactive optic neuritis. The fundi in some cases showed postneuritic atrophy. In others, the nerve heads showed almost no permanent changes. The unusual field changes in these cases were due only to enlargement of the blindspot. If the inflammatory process was sufficiently severe, nerve bundle defects and central or paracentral scotoma appeared, and the changes in some cases resembled those in cases of primary atrophy of the optic nerve. In cases of severe neuritis secondary atrophy of the optic nerve may ensue; in such cases the changes in the visual field become permanent. In the majority of cases of inflammatory processes of the optic nerve, vision became normal and the visual fields became normal or had defects limited to enlargement of the blindspot with slight changes for white or color after subsidence of the optic neuritis. Enlargement of the blindspot and a normal visual field for white associated with a concentrically contracted field for color were not found in cases of primary atrophy of the optic nerve and appeared characteristic of optic neuritis of long standing.

Sloan and Woods call attention to the fact that homonymous defects in the visual fields when present in patients with neurosyphilis appear to be dependent on such factors as cerebral trauma and arteriosclerosis with vascular accidents rather than on syphilitic involvement of the optic tracts or radiations.

SPAETH, Philadelphia.

EFFECT OF LIMITED COCHLEAR LESIONS ON COCHLEAR POTENTIALS AND MIDDLE EAR MUSCLE REFLEXES. H. G. KOBRAK, J. R. LINDSAY, H. B. PERLMAN and H. DUBNER, Arch. Otolaryng. **27**:59 (Jan.) 1938.

Researches on hearing have been made in the past by examining electrical potentials by the Wever and Bray method and also by the examination of conditioned reflexes. Another method has been the study of reflex contraction of the muscles of the middle ear in response to stimuli. The question arises as to the value of the different methods. Therefore, the effects of perforating lesions of the cochlea on electrical potentials and on muscle reflexes of the middle ear were compared. At first the phenomena were determined under normal conditions. Then the promontory was perforated with a small needle, allowing labyrinthine fluid to escape. Within a few minutes the acoustic response of the tensor tympani muscle disappeared, but the electrical potential response was undiminished, and in some cases even better. Although the apical portion of the cochlea had been destroyed, vibrations of a fork of 100 double vibrations, sound from higher-pitched tuning forks and the spoken voice were clearly demonstrated by the electrical potential method. A second series of animals was operated on. The perforation was allowed to close, so that there was no longer any escape of labyrinthine fluid. The reflex response of the tensor tympani muscle varied. Some animals showed diminished contraction and others no contraction to sound either by ear or by bone conduction. In all the animals the electrical response appeared to be of undiminished intensity. The authors' work demonstrates the independence of the cochlear electrical potential response from hydrostatic conditions within the cochlea. This finding is incompatible with the belief that such electrical potentials are dependent on the hairs in the cochlea. The role of electrical potentials in the process of hearing is not thoroughly understood. The authors, therefore, prefer to depend on "the reflex of the muscles of the middle ear [which] is a relatively simple biologic phenomenon, the anatomy and physiology of which have been known for many decades. Its use as an indicator of hearing in the experimental animal was proposed long after the reflex itself was thoroughly investigated. Finally the relation of the muscle reflex of the middle ear to the sensation of hearing has been carefully studied in the human being."

HUNTER, Philadelphia.

OBJECTIVE TINNITUS AURIUM. E. A. BREDLAU, Arch. Otolaryng. **28**:193 (Aug.) 1938.

Bredlau reports 3 cases of objective tinnitus and reviews similar cases described in the literature. Objective tinnitus may be either of vascular or of muscular origin. Spasmodic contraction of the eustachian tube is the chief causative factor in the muscular type of objective tinnitus; the immediate cause is the separation of the moist surfaces of the eustachian tube. Hysteria and neurasthenia have been hypothesized as predisposing or contributing factors. The vascular type of tinnitus is caused by the preternatural transmission of arterial or venous impulses to the ear resulting from (1) aneurysms, including arteriovenous aneurysms, both intracranial and extracranial, (2) hypertension, (3) vascular tumors of the brain and the ear, (4) coarctation of the aorta, (5) severe anemias, (6) pregnancy, (7) acute inflammatory disease of the ear and (8) vasomotor and endocrine disturbances.

J. A. M. A.

PARASAGITTAL MENINGIOMA ON THE RIGHT SIDE AND RIGHT LATERAL HOMONYMOUS HEMIANOPIA. B. POMMÉ, J. GUILLAUME and J. HAMON, Rev. d'oto-neuro-opht. **16**:383 (May) 1938.

A man aged 46 underwent successful removal of a meningioma from the upper part of the right parietal region. The area of attachment of the neoplasm was at the level of the longitudinal sinus. The tumor compressed the paracentral lobule downward and inward and descended along the falx as far as the corpus callosum. The paretic symptoms and crises of jacksonian epilepsy, from which the patient had suffered, were much ameliorated, but the hemianopia remained as before operation. The problem of the cause of the hemianopia remained unsolved. The authors suggest the possibility of multiple meningiomas, pressure transmitted to the visual pathways or a vascular lesion in the region of the tumor.

DENNIS, San Diego, Calif.

Diagnostic Methods

CHANGES IN THE GLUCOSE TOLERANCE TEST OCCURRING DURING AND AFTER INSULIN SHOCK THERAPY FOR SCHIZOPHRENIA. HERBERT FREED, ELEANOR FORTUNATO, S. DE W. LUDLUM and EDWARD A. STRECKER, Am. J. M. Sc. **196**:36 (July) 1938.

The authors report the results of their studies on the dextrose tolerance curves of 22 patients with schizophrenia who were treated with insulin shock and observed for varying periods after treatment. The significant features observed were: (1) the variation from normal of the dextrose tolerance curves before treatment; (2) the hyperglycemic (diminished tolerance) type of curve that occasionally occurred during the course of shock therapy, and (3) the hypoglycemic (increased tolerance) type of curve that occurred most frequently, more particularly at long intervals after treatment had been terminated. After a course of therapy there was a tendency toward a lower basal metabolic rate in the majority of the patients. The findings are probably not peculiar to schizophrenia in its therapeutic response to insulin therapy, nor are they of prognostic value.

MICHAELS, Boston.

LOCALIZATION OF INTRACRANIAL LESIONS BY ELECTRO-ENCEPHALOGRAPHY. D. WILLIAMS and F. A. GIBBS, New England J. Med. **218**:998 (June 16) 1938.

In order to ascertain the value of electroencephalography, Williams and Gibbs used the method with 80 unselected patients suspected of having intracranial lesions. The oscillographic records were made with an ink-writing instead of a cathode ray oscillograph, as used by Walter. Fifty of the patients showed abnormal cortical potentials with evidence of focal disturbance. The oscillographic records of 17 patients showed no cortical abnormality, and those of 13 were characteristic of epilepsy, without any evidence of a constant focus of discharge of slow waves. In the case of 13 of the 50 patients with foci of abnormal discharge operation was not performed, and the clinical diagnosis was too indefinite to verify the accuracy of the observations. In the remaining 37 cases verification of the position of the abnormality was possible. In 22 cases the lesion was seen at operation or necropsy; in 10 its position was established by unequivocal clinical observations, confirmed in 4 by roentgenographic evidence, and in 5 a defect was present in the skull as a result of previous trauma. In each of these 37 cases the position of the single focus of abnormal discharge corresponded closely with the site of the organic lesion. In the 22 cases in which the cerebral lesion was seen the correlation of the electroencephalogram with the operative and postmortem observations was striking.

J. A. M. A.

THE COLLOIDAL CARBON REACTION OF THE CEREBROSPINAL FLUID. A. ORTEGA IRAGORRI, Arch. de neurol. y psiquiat. de Mexico **1**:329, 1938.

Iragorri describes a modification of the technic used by Schube and Harms. Seven tubes are used, each containing constant amounts of distilled water, oxalic acid and diluted india ink. To six tubes spinal fluid is added in descending concentrations; the seventh is a control. The tubes are centrifuged for from ten to fifteen minutes at a speed of from 3,000 to 4,000 revolutions per minute, and may then be read directly. In the positive tubes the degree of flocculation is graded on a scale of from 1 to 4, 4 representing complete flocculation. Frequently the first tube shows less flocculation than the second or third.

Of 850 cases in which examination was made, a positive reaction was not elicited in any case other than one of syphilis. The test appears to be specific for syphilis and to be especially useful in doubtful cases.

KING, Princeton, N. J.

Basal Ganglia

INCREASED SPONTANEOUS ACTIVITY PRODUCED IN MONKEYS BY BRAIN LESIONS. C. P. RICHTER and MARION HINES, Brain **61**:1, 1938.

Richter and Hines studied the effects produced on the activity of monkeys by circumscribed lesions of the brain. The animals were studied by means of a special cage equipped with a recording device for measuring activity. The authors found that permanent overactivity is produced by gross unilateral or bilateral removal of the frontal poles of the brain. These lesions included the prefrontal cortex and the tip of the caudate nucleus and putamen. Unilateral removal of the prefrontal cortex produced only a slight increase in activity. Subsequent removal of the prefrontal cortex on the other side produced a great increase in activity. Unilateral and bilateral removal of areas 8 or of areas 10, 11 and 12 of Brodmann had little or no effect on activity. Bilateral removal of area 9 produced a definite increase in activity. Overactivity was definitely produced by removal of the tip of the caudate nucleus and putamen after the previous removal of the prefrontal cortex on the same side had failed to produce increase.

Degeneration of fibers and nuclei was studied in detail in 3 animals with cortical and striatal lesions. Analysis of fiber degeneration did not reveal any projection system not previously recognized by the recent studies of corticifugal systems arising in various portions of the prefrontal cortex.

These experiments bring definite proof of the regulation or control of activity through the frontal poles of the brain. They emphasize that the striatum as well as the prefrontal cortex is concerned and that of the latter area 9 plays the most important part. This result is not in agreement with the conclusions of Kennard and Ectors (1937), who expressed the belief that the increased activity which they observed was due to removal of area 8.

SALL, Philadelphia.

POST-TRAUMATIC PARKINSONISM. S. CHICHILNISKY, Semana méd. **1**:1420 (June 23) 1938.

Chichilnisky states that the existence of post-traumatic parkinsonism is proved. The diagnosis is made after verification of the following conditions: absence of any history of encephalitis; presence of violent cranial trauma and, generally, of a period of incubation of the disease; progressive uninterrupted evolution of the disease without appearance of mental symptoms, and a constitutional predisposition. Loss of consciousness does not necessarily accompany cerebral concussion, which may be demonstrated by other symptoms of shock. The period of incubation between trauma and the first appearance of the symptoms generally varies from eight to ten months. In rare cases it may be either longer or nonexistent. The disease develops without any remission. The syndrome is caused by hemorrhagic

lesions either in the optostriate nuclei or in the cortex of the frontal lobe. There is an evident correlation between post-traumatic parkinsonism and Marie's syndrome. The two syndromes generally coexist. From a medicolegal point of view the patients have permanent total incapacity.

J. A. M. A.

ETIOLOGIC FACTORS IN CHOREA MINOR. G. EDGREN, Acta med. Scandinav. **96**:43 (June 30) 1938.

Edgren points out that the most widely accepted opinion concerning the cause of chorea minor is that it has some connection with a rheumatic infection. Bacteriologic examinations of the brain, the spinal fluid and the blood of patients with chorea minor have yielded diplococci, staphylococci and streptococci. The pathoanatomic aspects of the brain vary; embolisms, congestion and small hemorrhagic foci have been observed. Moreover, attacks of chorea minor have been known to alternate with attacks of acute polyarthritis or endocarditis, and infections of the throat, measles, scarlet fever and influenza have been suspected of connection with chorea minor. Other investigators have suggested dysfunction of the parathyroid glands and psychic or physical traumas as causal factors of chorea minor. The majority of investigators regard hereditary predisposition as an important factor in the development of chorea minor, and Edgren reports the case of a girl with chorea minor whose three siblings were also subject to these attacks. Moreover, the mother of these siblings had had attacks of chorea gravidarum in the course of several pregnancies. The erythrocytic sedimentation speed of a large percentage of patients with chorea minor was either normal or slightly increased. Edgren reaches the conclusion that the cause of chorea minor has not been fully explained. Many factors indicate that chorea minor is not a definite disease entity but a syndrome with various causes. Hereditary predisposition probably plays an important etiologic role.

J. A. M. A.

Encephalography, Ventriculography and Roentgenography

ENCEPHALOGRAPHIC ASPECTS OF EPILEPSY IN CHILDREN. R. RUGGERI, Pediatria **46**:397 (May) 1938.

Ruggeri made encephalograms of 59 children and 2 adults with epilepsy. He found that the most frequent alteration shown by the encephalogram is enlargement of the ventricles alone or combined with dilatation or lack of filling of the subarachnoid spaces. The encephalogram in cases of hemiparesis showed bilateral asymmetric enlargement of the lateral ventricles, displacement of the ventricular system toward the less affected side and alterations of the subarachnoid spaces. In cases of bilateral hypertonia with pyramidal symptoms and epileptic dementia the encephalogram showed great bilateral enlargement of the lateral ventricles and alterations or absence of the subarachnoid spaces. The lateral and third ventricles were enlarged in patients with epilepsy, with changes of the character found in pyknolepsy. In a case of grave amblyopia the occipital poles of the lateral ventricles were greatly enlarged. In 2 cases of grave familial amblyopia in adults there was diffuse cortical atrophy. In the author's group, 20 patients were intellectually normal. The encephalogram was normal in 8. It showed alterations of the type of hemiparesis in 4, diffuse cortical atrophy, especially in the parieto-occipital zone, in 2; atrophy of the vertex in 1 and ventricular dilatation in 5. There were 17 cases of idiocy. In 11 of these cases there was great enlargement of the ventricles, in 4 of which there was also cortical atrophy. In 1 case of microcephalus and 1 of congenital syphilis the subarachnoid spaces were insufficient, and the right ventricle was deformed. The encephalogram was normal in 2 cases of tuberous sclerosis. It showed asymmetric enlargement of the lateral ventricles, one of which was greatly deformed. In an epileptic idiot the air failed to enter the ventricles and the subarachnoid spaces. The author found no relation between the frequency and intensity of the attacks and the aspect of the encephalo-

gram. As a rule the encephalograms which show great changes are of patients with extreme mental derangement. Patients with encephalograms which show slight or no pathologic changes react well to the sedative treatment (barbital or bromide), especially if given without interruption, even in small doses. The author concludes that encephalography is of value in the etiologic diagnosis of epilepsy and as a guide in determining the type (sedative, medical or surgical) of treatment.

J. A. M. A.

EXPOSURE TO SHORT WAVE THERAPY AND ITS EFFECT ON THE HEMATOENCEPHALIC BARRIER. R. GLAUNER and E. SCHORRE, Ztschr. f. d. ges. Neurol. u. Psychiat. **162**:551 (May) 1938.

Glauner and Schorre showed in previous studies that there is an increase in the protein and sugar content of the spinal fluid after short wave therapy. The meningeal permeability was studied by comparing the values for the sugar content of the blood and those for the spinal fluid by the trypan blue method and the Walter bromide procedure. Rabbits were used exclusively in these experiments. Although the values for the spinal fluid sugar were high, those for blood sugar were within normal limits. Trypan blue injected subcutaneously did not color the spinal fluid or tissue of the central nervous system, but penetrated the choroid plexus. All the organs of the body were colored with this dye. Comparison of the bromide quotients before and after treatment showed no significant difference. These studies show therefore that short wave therapy has no effect on the hematoencephalic barrier or the meningeal permeability. It also indirectly indicates that this barrier involves something more than the permeability of the meningeal and cerebral blood vessels, for it has been shown that there is considerable hyperemia of these blood vessels during exposure to short wave therapy. Diathermy applied to the heads of rabbits failed to produce the changes in the spinal fluid noted after short wave therapy.

SAVITSKY, New York.

Diseases of Skull and Vertebrae

HEMANGIOMA OF THE VERTEBRAL COLUMN. I. S. ROSENTSWEIG, Sovet. psikhonevrol. **14**:47, 1938.

According to Rosentsweig, hemangiomas of the vertebral column are benign vascular neoplasms developing frequently on the basis of a congenital anomaly of the vascular system. The great majority of these tumors are observed accidentally at necropsy. Hemangiomas only rarely give rise to clinical manifestations. They are capable, however, of producing a clinical picture of compression of the spinal cord. Of the 5 patients observed by the author, 4 presented symptoms of compression of the spinal cord. The diagnosis of hemiangioma of the vertebral column is possible only on the basis of roentgenologic examination. Hemangiomas causing compression of the cord may be treated by operative intervention or by roentgen irradiation. The former has a higher mortality because of profuse bleeding. Roentgen irradiation has been widely used in treatment of this condition, with gratifying results. The author reports cure in 3 of his 4 patients so treated and improvement in the fourth.

J. A. M. A.

Society Transactions

PHILADELPHIA NEUROLOGICAL SOCIETY

JOSEPH C. YASKIN, M.D., *President, in the Chair*

Regular Meeting, Nov. 18, 1938

PATHOLOGIC PICTURE AND PATHOGENESIS OF EQUINE ENCEPHALOMYELITIS IN THE GUINEA PIG. DR. LESTER S. KING, Princeton, N. J. (by invitation).

The histologic changes in the guinea pig following inoculation with equine encephalomyelitis virus by various routes are described in detail, and their histogenesis is traced. Distinctions are made between inflammatory and degenerative lesions, the former being more intense with peripheral and the latter with intracerebral inoculation. Analysis of the distribution of lesions in serial sections shows that the virus circulating in the blood usually attacks the brain directly through the walls of blood vessels.

This paper was published in the *Journal of Experimental Medicine* (**68**:677 [Nov.] 1938; **69**:675 and 691 [May] 1939).

DISCUSSION

DR. J. C. YASKIN: May I ask Dr. King whether in his experimental work there was involvement of systems other than the nervous system?

DR. LESTER S. KING: Yes. The virus can be recovered from various organs; even after a blood test has given negative results the liver and adrenal glands, and sometimes the kidneys, still contain virus, although they do not show any lesions. The lung is frequently the site of pneumonia.

DR. HELENA C. RIGGS: I was interested in the spread along the olfactory system in the guinea pig. This system in the guinea pig is very active and therefore should be highly vascularized. Is it not possible that spread may occur not along related neural pathways but, because of the damage to the blood-brain barrier, in the areas which are most active functionally, and therefore are most richly supplied with blood?

DR. LESTER S. KING: I am not sure that I understand the question. I say that the virus spreads along the nerve paths because it is only by this hypothesis that one can offer a reasonable interpretation of the selective distribution of these lesions. As to the vascularity of one system as compared with that of another—the degree does not differ sufficiently, it seems to me, to afford an alternative explanation.

DR. HELENA C. RIGGS: I refer to some of my experimental work with insulin in animals. The damage is in the same areas as those Dr. King showed; of course, in the case of insulin there is only a pure shock phenomenon. Since the damage occurs with both virus and nonvirus agents, it seemed that the common factor might be the greater functional activity, and therefore the greater vascular supply, of the areas affected.

DR. LESTER S. KING: Although certain writers have expressed a different opinion, I agree that the particular lesion is not due to action of a virus. It is nonspecific and must be explained on a vascular basis, but it is nonspecific because the animal is sick, not because it is sick with this particular disease.

DR. F. H. LEWY: Last week I saw specimens in a case of human encephalitis occurring during a recent epidemic in Boston. These pictures from the guinea pig look much like those from the patient, except that the human lesions appear to be very severe.

DR. M. W. THORNER: Can one distinguish this virus from other viruses which affect the nervous system, such as those of encephalitis and poliomyelitis?

DR. LESTER S. KING: One can distinguish one virus from another by two or three methods. One is the degree of animal susceptibility. It is known that poliomyelitis attacks monkeys and not any other laboratory animal. Then there are serologic tests which form the basis for distinguishing one virus from another. As far as I know, there is no really valid objection that can be brought against the reliability of these tests. The virus of equine encephalomyelitis will not neutralize any other and, in turn, will not be neutralized.

INTRADURAL SPINAL LIPOMAS: REPORT OF A CASE, WITH COMMENTS ON THEIR PROBLEMATIC ORIGIN AND UNUSUAL PATHOLOGIC CHARACTERISTICS. DRS. GEORGE WILSON, HARVEY BARTLE and JAMES S. DEAN.

A large intradural cervical and upper dorsal spinal lipoma occurred in a woman aged 21. Clinically, the condition was not associated with other congenital defect, presented no enlargement of the spinal canal roentgenologically, manifested its presence relatively acutely and presented little evidence of block with the Queckenstedt test. At operation, performed by Dr. Temple Fay, the substance of the cord and the tumor were relatively indistinguishable; the dura was split, a biopsy specimen was taken, and the tumor was not removed. Death occurred approximately two months after the operation. Pathologically, the tumor was a typical lipoma, entirely subdural and apparently arising from the pia on the surface of the cord. Its free surface was encapsulated and appeared to consist of thickened pia. It was not clearly demarcated from the substance of the cord, but appeared to arise from the pia and to grow away from, rather than to "invade," the parenchyma of the cord. Various current theories of the origin of intradural lipomas are presented. In discussing the histogenesis of intradural lipomas, reference is made to a recently encountered mixed tumor of mesodermal derivatives lying subpially between the two mamillary bodies, which consisted of bone, fat and connective tissue.

DISCUSSION

DR. HELENA C. RIGGS: The suggestion that these tumors may have arisen from embryonic rests is of interest. Congenital malformations of the nervous system frequently have been reported in conjunction with microcephaly, spina bifida and other gross somatic defects. However, malformations in the cytoarchitectonics of the brain may exist without evidence of somatic maldevelopment and are compatible with average, or even superior, mental development. In cases of mental disease, particularly, there are numerous evidences of incomplete migration and maturation. This appears to establish a real basis for Dr. Burr's often repeated dictum of "poor protoplasm" in such cases.

The most conspicuous heterotopias are collections of large ganglion cells, usually immature, between the anterior pillars of the fornix at the point of attachment of the choroid plexus, in the infundibular stalk and in the area postrema.

I believe that the presence of such heterotopias is of more than academic interest. In the light of the trend toward electrophysical interpretation of neural integration, the presence of such congenital malformations may contribute to an understanding of the disorders of neural function that today are called mental disease.

CHEMICAL AND PHARMACOLOGIC STUDIES ON DISEASES OF MUSCLE. DR. A. T. MILHORAT, New York (by invitation).

METABOLISM OF CREATINE AND CREATININE

The material in this portion of the paper has appeared in previous issues of the ARCHIVES (Milhorat, A. T., and Wolff, H. G.: Studies in Diseases of Muscle: I. Metabolism of Creatine and Creatinine in Progressive Muscular Dystrophy, ARCH. NEUROL. & PSYCHIAT. **38**:992 [Nov.] 1937; III. Metabolism

of Creatine and Creatinine in Myasthenia Gravis, Including a Study of the Excretion of Nucleosides and Nucleotides, ibid. **39**:354 [Feb.] 1938; IV. Metabolism of Creatine and Creatinine in Muscular Wasting Subsequent to Disease of the Nervous System, ibid. **40**:663 [Oct.] 1938; V. Metabolism of Creatine and Creatinine in Myotonia Congenita, Myotonia Atrophica, Myotonia Congenita, Dystonia Musculorum Deformans and Paralysis Agitans, ibid. **40**:680 [Oct.] 1938).

PROSTIGMINE AND PHYSOSTIGMINE IN THE TREATMENT OF MYASTHENIA GRAVIS

The choline esterase activity of the blood serum of patients with myasthenia gravis or muscular wasting is normal. Spontaneous changes in muscular weakness in patients with myasthenia gravis are not accompanied by changes in the esterase activity. Both prostigmine and physostigmine depress the esterase activity; this decrease is often accompanied by a striking improvement in muscular function in such patients.

Prostigmine has more effect on striated muscle and less effect on other structures than has physostigmine and is superior for treatment of myasthenia gravis. Patients seriously ill with the disease often require increasing amounts of prostigmine, and the esterase activity has to be kept at progressively lower levels. It appears that the muscles of patients fatally ill with myasthenia gravis become increasingly refractory and require increasing cholinergic stimulation for contraction. In such patients a greater depression in the esterase activity is required for clinical improvement. The refractoriness in certain instances may be of such a degree that the therapeutic effects of prostigmine are slight and of short duration. Patients receiving large amounts of prostigmine should be given sufficient amounts of atropine to abolish the undesirable side effects of the prostigmine. When large amounts of prostigmine are given an exacerbation of muscular weakness often occurs at the time that the esterase activity is returning to its previous level. This increase in muscular weakness often occurs at levels of esterase activity that are lower than those before the drug was given. Moreover, the reduction in the esterase activity required for clinical improvement is greater at this time. This increased refractoriness of the muscles induced by excessive amounts of prostigmine may be of importance in the management of the seriously ill patient.

DISCUSSION

DR. G. GAMMON: I was much interested in the lack of complete correlation between changes in esterase activity and muscular weakness. Dr. W. C. Stadie has studied the effect of prostigmine on muscle. In therapeutic doses it does not inhibit esterase activity in muscle. I wonder if Dr. Milhorat has any ideas on the chemical effects of this drug.

DR. A. T. MILHORAT: The effect of prostigmine on the choline esterase in blood serum is definite, and it is surprising that the drug should have no effect on the choline esterase in muscle.

DR. J. C. YASKIN: In what percentage of cases did myasthenia gravis fail to respond to prostigmine?

DR. A. T. MILHORAT: I have no definite statistics, but I believe that the results can be summarized as follows: Patients who are moderately or slightly ill usually respond well. Patients who have considerable muscular weakness and fatigability may respond well, but often in such patients the muscular weakness is more pronounced after the therapeutic effects of the drug have worn off than before the drug was given. In patients who are seriously ill, especially those with the rapidly fatal form of the disease, prostigmine has less effect on the muscular symptoms. Moreover, the duration of these effects is short. As the disease progresses larger doses of the drug are needed, and the duration of the effects becomes shorter.

DR. ALEXANDER SILVERSTEIN: Has pregnancy any effect on the clinical picture of myasthenia gravis? A patient of mine became pregnant, and after the second month practically all her symptoms disappeared. After parturition the baby died; the patient's symptoms returned; two or three years later she became pregnant,

and, again, after the second month of pregnancy her symptoms practically disappeared. Now, after the second pregnancy, she is progressing satisfactorily with about one-third the quantity of prostigmine she needed before.

DR. A. T. MILHORAT: I have not observed any patient during pregnancy. Most female patients give a history of exacerbation of weakness during the menstrual period. Moreover, the therapeutic effects of prostigmine are less at that time.

DR. M. W. THORNER: Has Dr. Milhorat had experience with guanidine? I believe he alluded to it.

DR. A. T. MILHORAT: Yes. The results have not been convincing. I am anxious to know whether guanidine will help the seriously ill patient who has become refractory to prostigmine. Guanidine appears to lower the threshold of muscle to cholinergic stimulation. It is interesting that the choline derivatives are of little value. The defect in myasthenia gravis probably is in the muscles. They appear to have become refractory to cholinergic stimulation. It is apparent that a better therapeutic agent is needed for the treatment of patients who are seriously ill.

DR. ALEXANDER SILVERSTEIN: In a patient who is fatally ill, is there any relationship to enlargement of the thymus?

DR. A. T. MILHORAT: One patient, data concerning whom were presented, had a rapidly fatal form of the disease. At autopsy an enlarged thymus was seen. I believe that about 20 per cent of all patients with myasthenia gravis examined post mortem have an enlarged thymus.

DR. J. C. YASKIN: What success did Dr. Milhorat have with quinine? With the 3 patients I treated I did not have good results.

DR. A. T. MILHORAT: I believe quinine is a valuable drug in certain instances of myotonia congenita, but in the patients whom my colleagues and I have treated undesirable side effects of the drug usually appeared when doses large enough to remove the myotonia were given. We started with 5 grains (0.325 Gm.) of quinine sulfate three or four times a day. Most patients complain of buzzing in the ears when they take 15 or 20 grains (0.975 or 1.3 Gm.) daily. During the last year or more I have used quinine to decrease muscular rigidity in paralysis agitans. In a few patients the muscular rigidity was so pronounced that swallowing was difficult and there were muscular pains. Quinine was found to be useful in some cases. In certain cases sufficient amounts of quinine could not be given because of side effects of the drug. The fact that patients with this type of muscular rigidity responded almost as well as patients with myotonia congenita is against the view that quinine has a specific effect in myotonia congenita.

THE MUSCULAR WEAKNESS OF FAMILIAL PERIODIC PARALYSIS. DR. GEORGE D. GAMMON.

Severe attacks of familial periodic paralysis are accompanied by lowering of serum potassium (Gammon, G. D.: *Proc. Soc. Exper. Biol. & Med.* **38**:922, 1938. Gammon, G. D.; Austin, H. J., and others: *Am. J. M. Sc.* **197**:326, 1939). Since there is no excessive elimination of potassium salts prior to or during the seizure, the decrease in serum potassium indicates a shift of potassium from the serum to some other body fluid or tissue. Gammon, Austin and others (*Am. J. M. Sc.*, to be published) have suggested that the shift may occur to muscle in response to an alteration in muscle metabolism, which itself is responsible for the weakness and which requires potassium for its correction. According to this view, the defect is considered to be in the peripheral structures rather than in the central nervous system. Pudenz, McIntosh and McEachern (The Role of Potassium in Familial Periodic Paralysis, *J. A. M. A.* **111**:2253 [Dec. 17] 1938), on the other hand, expressed the belief that the abnormality is central rather than peripheral because recovery occurred after injection of potassium chloride into the general circulation even when the circulation of the paralyzed part was obstructed and

no new potassium allowed to enter. This view, however, does not account for an old observation in the literature, namely, that the muscle is electrically inexcitable during the attack.

It seemed important to test this observation; in order to do so, my colleagues and I studied the excitability of muscle during attacks induced by epinephrine. Stimulation over the motor point of the extensor muscle of the third finger was employed and movement of the finger recorded kymographically. Electrical stimulation in the form of simple induction shocks, 60 cycles alternating current, and repetitive pulses of short duration with variable frequency were employed. We can confirm the statement in the older literature concerning inexcitability of the muscle during a seizure. The current could be raised to a level at which distant muscles contracted strongly without evidence of contraction in the paralyzed muscle.

Analysis of the earlier phases of the weakness showed that the threshold gradually rose; there was failure of response to single shocks at the time tetanus was effective; later, responses were not obtained at frequencies below 15 cycles per second, and finally the tetanus (frequencies up to 165 cycles) became ineffective. It is thus apparent that the muscle could not be stimulated during the attack.

We next studied the effect of anoxemia on the response of the weakened muscle, since the irritability of normal peripheral nerve rises during anoxemia. When there was no attack the curve of increased excitation was normal. During an attack, however, the development of hyperexcitability was delayed and lasted longer than normally. During an attack in which the muscle was completely paralyzed, after a period of obstruction of the circulation for ten minutes, both voluntary strength and electrical excitability returned and continued to increase for another ten minutes, almost normal strength being regained. The return of voluntary power under these circumstances must be due to correction of a peripheral fault. In view of the finding that the contraction may return during circulatory obstruction, caution must be observed in attributing the effect to a drug administered under the same experimental conditions.

In a further study of the results of stimulation at various frequencies and of the effect of tetanus on a twitch, the responses were found not to be analogous to those described for drugs which block transmission at the myoneural junction.

The failure of electrical excitability of muscle is the strongest argument favoring a peripheral defect in the attacks of this disease. Other evidence which argues less directly for this point of view is the extreme focal character of the weakness. Finally, the simultaneous return of the contraction of paralyzed muscle, both on electrical stimulation over its motor point and on voluntary effort, during arrest of the circulation to the limb indicate the correction of a defect at the periphery.

DISCUSSION

DR. A. T. MILHORAT: I have had the opportunity of making careful studies of mineral balance in a patient with familial periodic paralysis. The studies were made after a series of attacks. Unfortunately, the patient had no attack during the period of study. However, the findings were none the less interesting. The balances of calcium and magnesium for various levels of intake were normal. The balance of phosphorus, however, was abnormal during the entire period of observation of forty-two days, in that there was persistent loss of this mineral. I have studied patients with other types of muscular disease; in all the mineral balances were normal. Since the loss of phosphorus occurred without concomitant loss of calcium, it is probable that the phosphorus came from a source other than the bones. This site was probably the muscles. Brand found a lowered concentration of phosphorus in the muscle of a patient with familial periodic paralysis, although no muscular wasting was present. Levels of potassium as low as those occurring in patients with familial periodic paralysis have been observed in diabetic patients receiving insulin. There must be a factor in addition to the concentration of the potassium, and these studies suggest that it is the phosphorus content of the muscle.

JOSEPH C. YASKIN, M.D., *President, in the Chair*

Regular Meeting, Dec. 16, 1938

TUMOR IN THE POSTERIOR FOSSA (?): REPORT OF A CASE. DR. ALFRED GORDON.

F. P., aged 54, was gassed in the World War. Until March 1919 he was kept in a base hospital. In 1922, while at work on a construction job, he first felt numbness on the right side and observed that he was walking toward the right. These two symptoms, together with occasional dizziness, continued during a period of ten years, up to 1932. At that time new symptoms developed, which completely disabled him for work. He suffered from paroxysms of unusually severe pain in the right temporo-occipital region, which was sometimes accompanied by dizziness.

As all the symptoms described are still present, they may be summed up as follows: There is slight weakness of the right arm and leg; the knee jerks cannot be elicited, but there are no pathologic reflexes. There are loss of vibratory sense in the legs; definite hypesthesia and hypalgesia of the right side of the face and pharynx, with quantitative diminution of smell in the right nostril, and deafness on the right. The gait shows a tendency to veer to the right, especially when the eyes are closed. There are falling to the right when the patient is standing with the eyes closed; dysmetria in the right arm and leg in all tests; adiadokokinesia on the right; right unilateral diplopia; paroxysms of unusually severe pain on the right side of the head; attacks of "absences," which may last for hours, and attacks of irresistible aggressiveness.

Encephalographic studies showed dilatation of the third and left lateral ventricles and numerous areas of increased and decreased prominence of the subarachnoid pathways.

The numerous symptoms on the right side indicate involvement of the cerebellum on that side. On the other hand, involvement of several cranial nerves on the same side points to a disorder not limited to the cerebellum. There is partial involvement of the following nerves on the right side: the fifth nerve (pain and marked hypesthesia, with abundant perspiration over the right side of the face); the sixth nerve (diplopia on the right side, due to partial involvement of the nerve to the external rectus muscle or of a portion of its nucleus); the eighth nerve (total deafness on the right); the olfactory apparatus; the chorda tympani nerve (difficulty in differentiating taste), and the sensory supply of the pharynx (hypalgesia).

Hence there is a pathologic state on the right side of the base of the brain, involving the nuclei of several cranial nerves and the right hemisphere of the cerebellum.

In order to determine the nature of the lesion, the following facts must be taken into consideration: the long course of the disease, the gradual and progressive development of the various symptoms and the history of paroxysms of severe headache; these all suggested at first the possibility of a cerebellar tumor. However, the absence of hypertensive effects; the persistence of normal eyegrounds for sixteen years; the paroxysmal (discontinuous) character of the headache, between attacks of which the patient is not particularly disturbed in his daily life in spite of the persistence of all the other objective manifestations; the absence of vertigo or vomiting; the appearance of the patient, free from evidence of suffering—all these circumstances render the diagnosis of tumor doubtful.

Déjerine and Thomas (*Nouv. iconog. de la Salpêtrière* **13**:330, 1900) called attention to a disorder which they named "olivopontocerebellar atrophy." Since, many observers have corroborated the existence of this syndrome. While it is rare in pure form, as other structures may become involved simultaneously or subsequently so that it is with difficulty differentiated from disease of the vicinity, cases have been recorded which are identical histopathologically with those described by the original authors. With the dilatation of two ventricles and, especially, the numerous areas of increased and decreased prominence of the

subarachnoid pathways, which are frequently observed in patients with cortical atrophy associated with arachnoiditis, the presumption in the present case is strongly in favor of a similar diagnosis. Since the symptoms are chiefly on the right side, I believe that this case is one of olivopontocerebellar atrophy on the right side. The irregular distribution of the areas of atrophy, although predominantly on the right side, suggests a vascular origin. This may be corroborated by the arteriosclerotic condition of the retina observed in both eyes, and by the fact that cortical cerebellar atrophies occur at an advanced age. The illness in this case has lasted many years and began with mild cerebellar manifestations, to which, in time, were added the unilateral disorders of the cranial nerves and more serious cerebellar phenomena. Special emphasis is laid on the differential features of tumor and cortical atrophy and on the value of encephalographic studies in doubtful cases. The latter diagnosis may be, and because of the complexity of the signs perhaps is, the deciding factor when surgical treatment is contemplated.

As to the etiologic factors in cortical atrophy: The records of the few published cases show a variety of causes: intoxications, such as those due to lead, carbon monoxide and alcohol; trauma, and infectious processes. In my case there was a history of being gassed, followed early by the onset of two cerebellar symptoms. There was also a history of moderate alcoholism during the same period. The pathologic process in all cases of cortical atrophy begins in adult life and is probably abiotrophic.

DISCUSSION

DR. F. C. GRANT: This man was in the University Hospital and there presented the same diagnostic difficulties; my associates and I reached about the same conclusion as did Dr. Gordon. It seemed unlikely that a man could have had such symptoms for sixteen years as the result of a mass lesion, such as a tumor, for in that time he certainly would have shown more evidence of increased intracranial pressure. A cold caloric test was performed; strangely, most of the symptoms were on the right side, so it was hard to account for the picture. The encephalographic findings were mostly those of bilateral atrophy of the cord. This was entirely compatible with the diagnosis of arteriosclerosis, and there was no indication for surgical intervention.

That the patient might have an anxiety neurosis was suggested by certain factors in the history.

DR. A. M. ORNSTEEN: It may sound silly and unlearned to ignore an encephalogram, but there is much in this case to suggest a benign condition which is psychogenic. I do not think a person can have double vision in one eye unless there is a gross disturbance in the cornea following injury; then it is not true double vision; it does not occur if the eye is turned to one side. This patient may have a broken image due to an injury, but that is not double vision. He is said to have loss of hearing on the right side; yet when Dr. Gordon spoke to him he turned his right ear toward him. The man is supposed to have had cerebellar symptoms on the right side for sixteen years; if so, by now he would not be able to walk as well as he does; when he walked out, he gesticulated with his right hand instead of the left. If he had had cerebellar involvement for sixteen years, I do not believe he would have done that.

I believe this is a case of hysteria. The man was in the army; the symptoms started in 1922. I should like to know if he has been a recipient of indemnities from the Veterans' Bureau.

DR. B. J. ALPERS: Are there any signs to support the diagnosis of cortical atrophy? It is dangerous to make such a diagnosis from an encephalogram alone, for I believe that the evidence is highly misleading. One can find nothing to support it at autopsy.

DR. ALFRED GORDON: All know that organic diseases are often associated with manifestations of hysteria. The tendency to ascribe everything to hysteria is difficult for me to understand. I acknowledge the anxiety state the man has been

in. He has been a sufferer, unable to secure a job, has a family and has shown anxiety with fear of the future.

One must consider the paroxysms of pain that could be relieved only by draining the spinal fluid. Is it hysterical pain that disables him completely? There are also the loss of vibratory sense in the lower extremity and the loss of knee jerks. Are these due to hysteria? How can one ascribe to hysteria all the symptoms of a distinct cerebellar type and involvement of the cranial nerves on the right side? Davidson and Wechsler described cases in which the symptoms were identical, but on the left side. Autopsy showed involvement of the cerebellum and nuclei of certain cranial nerves. The man has psychogenic symptoms, but there can be no doubt that he has an organic disturbance also.

ANALYZING FUNCTION OF THE LABYRINTH. DRS. M. OPPENHEIMER and E. SPIEGEL.

Conditioned reactions to angular acceleration on rotation around a vertical axis are easily obtainable. Their threshold lies at or below 2 to 3 degrees per second per second. Dogs were also trained to discriminate the direction of the accelerated rotation. The receptor mechanism of these reactions was analyzed. While the loss of the labyrinths may be compensated, as far as the development of conditioned reactions to angular acceleration is concerned, the discrimination of direction of rotation around a vertical axis remains absent in labyrinthectomized dogs on rotation at low acceleration. Discrimination of direction of rotation in the horizontal plane at low acceleration seems, therefore, to be an important criterion of the analyzing function of the labyrinth.

ACUTE SYPHILITIC MENINGITIS. DRS. D. TURNOFF and MELVIN W. THORNER.

The concept of a syndrome of acute meningitis due to syphilis is almost entirely a clinical one. Nineteen cases have been reviewed in tabular form and others in more detail by means of case histories. The major criteria for selecting the cases were: (1) clinical evidence of acute meningitis consisting in nuchal rigidity, Kernig and Brudzinski signs and increased cell count of the spinal fluid; (2) serologic evidence in the spinal fluid of the presence of syphilis, and (3) absence of any other factors which might be responsible for the syndrome.

The importance of correct diagnosis lies in the relatively good prognosis and effectiveness of competent treatment.

DISCUSSION

DR. S. B. HADDEN: I congratulate Drs. Turnoff and Thorner for this excellent presentation, although I am not in accord with their belief that acute syphilitic meningitis is a common disease. I do not believe that their criteria for the establishment of a diagnosis are sharply enough defined, and I suggest that the following diagnostic criteria be fulfilled in all cases before a diagnosis of acute syphilitic meningitis is made: (1) the onset should be acute; (2) there should be elevation of temperature; (3) the patient should not have had any preceding neurologic symptoms of long standing; (4) the meningeal symptoms should be acute and the most prominent feature of the case; (5) the spinal fluid cell count should be several hundred.

If these criteria were followed in this group of cases, I am sure that the number would be decreased considerably, in keeping with the impression that acute syphilitic meningitis is a relatively uncommon disease.

I do not believe that headache, rigidity of the neck and an increased cell count of the spinal fluid constitute the clinical evidence of acute syphilitic meningitis. If this were so, dementia paralytica and almost every other variety of neurosyphilis would at some phase be regarded as acute syphilitic meningitis. During the secondary stage of syphilis, intense headache, rigidity of the neck and photophobia are not uncommon, but these do not constitute acute syphilitic meningitis. The statistical study, like most such studies, loses much of its value because diagnostic

criteria vary with the intern or the attending physician. Arguments against the diagnosis, as established in these cases, are not purely academic, for treatment will vary accordingly. A cell increase in the spinal fluid is associated with almost any lesion of the central nervous system, especially one close to the surface. When a gumma is accountable for the increase in the cell count of the spinal fluid and the additional meningeal symptoms the treatment will differ considerably from that when the meningeal symptoms are due to acute syphilitic meningitis.

In Merritt's series, I believe that his diagnostic criteria were rather loose and that this accounts for the large number of cases reported. Stokes, using more critical criteria, reported but 3 cases up to 1934. I have observed but 1 case that I considered to be an instance of acute syphilitic meningitis. I have encountered many that could be so regarded if the criteria of Drs. Thorner and Turnoff were used.

DR. J. C. YASKIN: What was the treatment in this case?

DR. S. B. HADDEN: It was not successful. The patient died. Neoarsphenamine was given every other day, without beneficial effect.

DR. MELVIN W. THORNER: In the cases reviewed in the literature and in those we have reported, fever was generally slight or absent. This point is important and valuable in differentiating acute meningitis due to the spirochete of syphilis from meningitides caused by other agents, since the majority of meningitides are associated with marked elevation of temperature.

The cytologic reactions of the spinal fluid are likewise important. The range of total cell counts is wide, but it must be remembered that cell counts of over 2,000 do not rule out syphilis as a cause of acute meningitis.

The incidence of lesions of the cranial nerves in our cases is much lower than that in the series reported in the literature. This is probably explained by the exclusive criteria we adopted in selecting our group. The series reported by Merritt and Moore is more inclusive, while that of Nonne, in which the disease was described as acute meningitis of the convexity, more closely resembled ours.

We agree with Dr. Alpers that the term "meningitis" is not wholly satisfactory. For the moment, we can offer no substitute word for the clinical syndrome of stiff neck, Kernig and Brudzinski signs and increased cell count of the spinal fluid.

LOCALIZED NONSUPPURATIVE ENCEPHALITIS ADJACENT TO A FOCUS OF INFECTION IN THE SKULL. DR. E. MILES ATKINSON (by invitation).

This paper was published in the March 1939 issue of the ARCHIVES, page 556.

NEW YORK NEUROLOGICAL SOCIETY

CHARLES A. MCKENDREE, M.D., *President, in the Chair*

Regular Meeting, Dec. 6, 1938

ACUTE INJURIES TO THE HEAD. DR. JOSEPH E. J. KING.

POST-TRAUMATIC SUBACUTE AND CHRONIC SUBDURAL LESIONS. DR. IRA COHEN.

A study was made of cases of subdural hematoma and hydroma in which operation was performed later than ten days after the injury to the head. The discussion is based on 25 cases of hematoma and 4 of hydroma. In the cases of hematoma, especially, the trauma was minor, usually an incident of everyday domestic life rather than an industrial accident.

On the basis of the history and physical signs as they are presented to the physician, the cases may be divided artificially into four groups: (1) those in which

the patient dates his trouble from and correlates it with the accident; (2) those in which the patient is suspected of having tumor of the brain but has forgotten, or at least does not stress, the trauma and the picture of an expanding intracranial lesion is presented; (3) those in which the patient comes into the hospital in stupor or semistupor after complaining of headache for a day or two and in which often no history of trauma is obtainable, and (4) those in which the outstanding feature is the profound mental alteration, with minimal signs of organic disease.

The inconstancy of physical signs was noted, as well as the absence of convulsions, alterations of the visual fields and profound disturbances of speech. The one common symptom was headache. There was alteration in consciousness in about two thirds of the patients; One half showed papilledema and bradycardia, and one third, meningeal signs.

The pressure of the spinal fluid was increased in 16 instances, and the fluid was xanthochromic in 10.

Failure to visualize the ventricles was frequent in the presence of a hematoma. This was as often noted by direct as by endolumbar injection of air. In 1 case the ventricular system showed no displacement. In the others there was a downward shift, as well as lateral displacement.

Simple evacuation by trephining proved to be sufficient in the majority of cases.

DISCUSSION

Dr. Israel S. Wechsler: This is an excellent and complete presentation, which invites little discussion and no differences of opinion. One can only stress a few points. The diagnosis, now that one has become "hematoma conscious," is being made on direct clinical evidence with increasing frequency. There was a time when it came as a surprise; now the neurologist and the neurosurgeon should be able to make the diagnosis with a fair degree of accuracy in the large majority of cases. Despite the fact that in some of Dr. Cohen's cases a history of trauma was not obtainable, it is perhaps the most important point in diagnosis. It would be difficult to make a diagnosis without a history of trauma, however slight. Dr. Cohen is right in saying that the trauma as a rule is trivial.

The second point is the fluctuation of symptoms. One sees patients who are comatose, sometimes deeply so, and for no apparent reason they come out of the coma, become fairly responsive and then relapse into unconsciousness. It is this fluctuation of consciousness which differentiates subdural hematoma from other expanding lesions, more particularly tumors of the brain.

A point which Dr. Cohen merely mentioned in passing is worth stressing, namely, that ipsilateral signs are not uncommon in cases of subdural hematoma, perhaps more common than in any other condition. I wonder why he did not stress more the need of making a bilateral trephine opening as a routine. I do not know whether all surgeons do that invariably, but it seems to me that bilateral trephining is advisable, for the laterality of the lesion cannot always be determined clinically.

I, too, believe that the diagnosis can be made without air studies in a large percentage of cases. Often, however, an encephalogram or a ventriculogram is of great help. As trephining is comparatively harmless, one can do it without recourse to the pneumographic procedure.

Dr. Foster Kennedy: I wish to be dogmatic: In every case in which subdural hematoma is suspected bilateral trephination should be done. Nothing will be lost by this; it is a minor operation; it does no harm; it does many persons much good. There is no use in hesitating.

Dr. Abraham Kaplan: There is little I can add to the comprehensive paper presented by Dr. Cohen this evening. However, it is well to stress a few points concerning this important subject. The subdural space is a potential one and has no circulatory or absorbing mechanism. When blood or subarachnoid fluid is trapped in this space, it interferes with the natural pathways of the cerebrospinal fluid; this may readily account for ventricular dilatation before operation in the cases cited by Dr. Cohen.

It is important to stress that accumulations of blood or fluid in the subdural space frequently must be diagnosed by exclusion. After careful consideration and elimination of such conditions as encephalitis, intracranial neoplasm, morphine poisoning, alcoholism and cerebral thrombosis, one must consider the diagnosis of a chronic subdural collection.

It has been the difficulty in previous years that now and then one was mistaken as to the side of the lesion; my colleagues and I, therefore, have adopted the routine of bilateral trephination, which Dr. Kennedy so firmly advocates. The accompanying slide illustrates the reason for earlier mistakes as to the side of the lesion. This represents a case of unrecognized chronic subdural hematoma; the convolutions on the side of the hematoma are relatively normal in appearance, whereas the convolutions of the opposite hemisphere appear much wider and more edematous —evidence in favor of compression against the under surface of the skull. The patient presented homolateral signs.

As Dr. Kennedy has pointed out, at the Bellevue Hospital we no longer hesitate to perform a bilateral trephination with the use of local procaine anesthesia, which can be done rapidly and with no ill effects on the patient.

The next slide shows the skull of a boy aged 6 years in whom we suspected a neoplasm or hematoma. Bilateral trephination over the postparietal regions preliminary to ventriculographic study disclosed a large chronic subdural hematoma on the left. In instances in which no hematoma is found one can readily proceed with ventriculographic examination to establish the diagnosis.

DR. THOMAS K. DAVIS: To me the most interesting part of Dr. Cohen's excellent paper is that which deals with hydroma. I am sure I am right in saying that less is known of this condition than of hematoma; even the term rolls off one's tongue with some difficulty; one is not nearly so accustomed to talking about hydromas. The first part of Dr. Cohen's paper states that much has been learned in thirteen years. Perhaps this is true of hematomas, but is it of hydromas? Clinically, hydroma and otitic hydrocephalus may sometimes be confused; perhaps Dr. Cohen would make his paper of broader scope if he were to add something about the differential diagnosis of the two conditions. As I understand it from a recent paper of Symonds (Otitic Hydrocephalus, *Brain* **54**:55, 1931; Hydrocephalic and Focal Cerebral Symptoms in Relation to Thrombophlebitis of Dural Sinuses and Cerebral Veins, *ibid.* **60**:531, 1937), the cause of otitic hydrocephalus is thrombosis, not always complete, of the superficial veins of the cerebrum, sometimes with partial thrombosis of the longitudinal sinus. In such a case papilledema is pronounced. The secondary collections of fluid are only in the subarachnoid spaces. One knows that the condition arises ordinarly from otitis, but according to Symonds it may come from an infection elsewhere, in a structure more remote than the ear.

In a patient whom I saw recently a collection of clear serous fluid lying anterior to the left cerebellar lobe followed a severe piercing wound in the ear. Used broadly, the term hydroma could be applied in this instance also. The condition was relieved by operation eventually, but a third operation was required. Dr. King could tell more about that, for he was the surgeon. Since repeated lumbar puncture can cure otitic hydrocephalus, is it of any aid in the treatment of hydroma?

DR. J. H. NOLAN: May I say that the diagnosis of subdural hematoma is probably made by exploration more often than by exclusion of other conditions? I am sorry that the subject of acute subdural hematoma was not stressed, for there are times when a patient is brought into the hospital with a severe injury to the head. All attempts at dehydration having failed to revive the patient, an exploration is in order.

One such patient was observed in the New York City Hospital. The man had sustained a severe injury to one side of his head. He began to improve under dehydration, but two days later again became comatose. The localizing signs

were on the side opposite the injury. Dr. Gross trephined and found an acute subdural hematoma. There was also a small laceration of the brain. The man recovered rapidly.

DR. SIDNEY W. GROSS: The problem of acute subdural hemorrhage is different from that of subacute and chronic traumatic subdural hematoma. Nevertheless, there are times when it is difficult to make a differential diagnosis between laceration of the brain with subdural hemorrhage and subacute subdural hematoma. The mechanism of the production of hematoma in some cases of traumatic origin is similar—there is a collection of blood which becomes encysted. The molecules of hemoglobin break down, and the encysted collection grows by osmosis. One does not operate on patients with acute subdural hemorrhages more often because most of them have severe lacerations of the brain, with a tremendous amount of hemorrhage. The laceration of the brain and the severity of the injury far overshadow the symptoms produced by the subdural hemorrhage. However, I think that an exploration is in order in the case of any patient who has sustained a severe injury to the head and, after a period of apparent improvement, presents focalizing signs or coma which one is sure is not the result of dehydration. The case Dr. Nolan mentioned was of this type. A man who had a severe injury to the head, complicated by alcoholism, improved after treatment. Six days later he became comatose, and there developed hemiplegia. When I saw him eight days after the injury he had a slow pulse, unilateral dilatation of the pupil and hemiparesis. At operation an encysted collection was seen between the two membranes, with a partially broken-down blood clot. After it was removed, a small laceration of the brain, with tearing of a cortical vessel, was disclosed. After operation the patient made a rapid recovery.

DR. JOSEPH E. J. KING: I agree with all that Dr. Cohen has said. He stated everything so plainly that one could not fail to understand. He laid emphasis on the slight or "forgotten" injury which is the causative factor in many subdural hematomas. Concerning the light blow which may cause a hemorrhage of this type, as well as the great number of times one's head is struck in such a manner, it is astonishing that more hematomas have not occurred.

In answer to Dr. Wechsler's question regarding bilateral trephination, I think Dr. Cohen would say that he assumed that this is done by practically all neurosurgeons. One probably learned to do this from experience in the past, in which in the majority of cases the trephination was performed first on the wrong side.

DR. IRA COHEN: I wish first to refer to Dr. King's remark that one learned to do bilateral trephination because the first opening was usually made on the wrong side. I prefer to make the initial trephine opening on the side opposite the lesion, if I am fortunate enough to have a patient with contralateral signs, because I routinely make bilateral trephine openings and I like to examine the normal side first so that I can devote the rest of the time to the side of the lesion.

In answer to Dr. Davis' question: I think that hydroma and otitic hydrocephaly are two entirely separate conditions. The so-called otitic hydrocephalus, of which little is known, is characterized, as seen in air studies, by internal hydrocephalus and, as seen on the operating table, by a small amount of fluid in the subarachnoid space, which constantly fills as one watches it. One is dealing with a sponge that is oozing fluid. On the other hand, in the so-called hydroma, fluid is outside the arachnoid but inside the dura. The brain is depressed 1 or 2 cm. below the dura. In a case I described ten or twelve years ago at a meeting of the New York Academy of Medicine, Section of Neurology and Psychiatry, the entire frontal lobe was so crowded back by fluid that it was possible, on turning down the flap, to visualize the optic nerve without touching the brain. From that patient, in the course of emptying the fluid at the time of operation and, subsequently, through the skull defect, there was removed about 2,500 cc. I think that the two conditions are different. In the one the fluid is beneath, and in the other outside, the arachnoid.

A Revised Classification of Mental Sequelae of Trauma to the Head. Dr. Karl M. Bowman and Dr. Abram Blau.

A. Primary traumatic mental disorders (mental disorders due primarily to trauma to the head)

I. Acute
Concussion syndrome
Traumatic coma

II. Subacute
Traumatic delirium
Traumatic Korsakoff or amnesic psychosis
Other types (to be specified), e. g., stupor, apathetic syndrome, twilight state, mixed type

III. Chronic
Post-traumatic disorders of personality
(*a*) Of adults
(*b*) Of children
Post-traumatic mental defects
(*a*) Special (to be specified), e. g., memory, aphasia, alexia, anemia
(*b*) Generalized
Mixed types
Punch drunk
Traumatic disorder with convulsion
Other types (to be specified)

B. Secondary traumatic mental disorders (mental disorders associated with or precipitated or complicated by trauma, but not due primarily to trauma to the head)

I. Psychoneurosis (type to be specified) with trauma to the head (e. g., conversion hysteria, anxiety state, terror neurosis, malingering)

II. Psychosis (type to be specified) with trauma to the head (e. g., dementia paralytica, psychoses due to alcohol, psychoses with cerebral arteriosclerosis)

III. Mental deficiency (amentia) with trauma to the head.

The classification of disease changes constantly as understanding of the etiologic and pathologic factors increases. This is particularly true with regard to mental diseases, knowledge of which has increased rapidly in the past few decades. At present there is a standard nomenclature of disease which has been adopted by medical associations and hospitals of this country (Standard Classified Nomenclature of Disease, New York, The Commonwealth Fund, 1935). The section on the classification of mental disorders has been agreed on by the American Medical Association, the American Neurological Association and the American Psychiatric Association. This classification has been published separately by the National Committee on Mental Hygiene, with explanatory notes to aid in making the correct diagnosis.

In the classification for mental conditions due to trauma, one finds that under the general heading "Psychosis Due to Trauma (Traumatic Psychosis)" the following subheadings occur:

Traumatic delirium
Post-traumatic personality disorder
Post-traumatic mental deterioration
Other types (*to be specified*)

We are of the opinion that the present scheme is inadequate and that it would be of value to neurology and psychiatry to revise the classification. A number of well known specific syndromes can be added, and it is also important today to include a place for those mental disorders in which trauma, in addition to other factors, assumes a secondary etiologic role.

A classification is not to be thought of as an outline which is fixed. It must serve practical purposes, and one should be prepared to revise certain portions from time to time. In general, it may be said that one of the greatest advances in medicine has been the change from a classification of descriptive type based on symptomatology to one based on etiology. Neuropsychiatry is still too much at the descriptive level, with relatively little knowledge of etiology. Meyer's concept of reaction types among mental disorders represents a significant advance. In the scheme of classification which we propose, we are thinking not of a series of varying disease entities but of a number of different mental syndromes which occur after an injury. In many cases the clinical picture may not be that of a pure syndrome and must be classified as mixed. Furthermore, from day to day one may see a fluctuation from one syndrome to another, with mixed periods of transition during the progress of the illness.

Before proceeding with the discussion of our classification, one must bear in mind that within recent years the role of trauma in the etiology of disease has assumed great practical significance. Previously, psychiatric schools of thought, like those in other branches of medicine, were interested mainly in direct causes. However, the development of compensation laws has led to the need for a reorientation of thought. The practical demands for medicolegal opinions concerning the partial, in addition to the complete, part played by trauma in the causation of an illness have required more consideration of the influences of trauma as an accessory factor. In neuropsychiatry this problem is particularly complicated because one must take cognizance of both organic and psychogenic factors, especially when the injury is directed toward the head and brain. With much available knowledge yet at the descriptive level, some so-called syndromes are not specific. In many instances neuropsychiatric syndromes may be caused by either organic or psychogenic agents, and constitutional factors are always important. The diagnosis of each neuropsychiatric condition must be approached with this threefold concept—that of the organic, psychogenic and constitutional factors—and the most that can be said in many cases is that there is a combination of all three, probably with especial emphasis on one factor. In the final analysis, each case must be judged separately after a complete investigation of the previous constitutional tendencies, the psychogenic shock and the specific physical effects of the trauma.

With the preamble of these limitations, we shall not discuss our classification. We start with the etiologic concept of a group of mental disorders due to trauma to the head. Trauma is used here in the accepted medical sense of a physical injury to some part of the body. This inclusive group is then classified under two main headings according to the etiologic status of the trauma, as a primary or as an accessory organic contributing agent. The primary traumatic mental disorders are those in which there is a fairly clear relation of the mental symptoms to organic injury to the brain, due primarily to direct or indirect impact of physical force to the head. The secondary traumatic mental disorders are those in which actual injury to the brain plays a variable part in the production of the pathologic changes and other factors—constitutional, psychogenic or organic—may play an even greater role.

The further subdivisions in the classification are then made on the basis of clinical symptom complexes, or reaction types. It will not be necessary to redefine many of these syndromes, since they correspond to similar reaction types described in the standard psychiatric textbooks.

DISCUSSION

DR. ISRAEL S. WECHSLER: The classification of mental sequelae of trauma to the head is difficult to discuss. It is an extremely important subject, and Dr. Bowman and Dr. Blau have done a service in bringing it up for discussion. It should be reviewed from time to time, all the more as one knows so little about it. One is still in the stage of descriptive classification in psychiatry. I fear that

psychiatrists continue to use not only Greek and Roman language but also ancient and medieval concepts. It is no discredit to psychiatry to admit the fact. In other branches of medicine physicians are far beyond that stage. It took many centuries to differentiate between the eruption of smallpox, measles, scarlet fever, chickenpox and acne, and many more centuries to learn pathology, etiology and treatment. Not knowing enough about the anatomy and physiology of the brain or about the pathways involved in the highest form of cerebration, namely, thinking, one is compelled to rely on descriptive or verbal classification.

The general quarrel that one has with the classification submitted is that it is too complex and detailed. The main task in the present stage of knowledge is to simplify. What the authors of the paper have done is to separate a great many syndromes which are in a measure related to trauma. The first heading, namely, concussion, is an old concept and really says nothing. It means "shaking up of the brain." Attempts have been made in recent years to throw out the word "concussion" entirely, to regard it as an organic condition and to substitute the word "encephalopathy." In many cases there are the symptoms of a neurosis, from which the condition cannot be differentiated clinically. Air studies frequently show changes in the ventricles and atrophy of the structures of the brain. One knows from examinations in many cases that minute hemorrhages frequently occur. It seems to me that the word concussion, if it is used at all, should be limited to an organic syndrome, irrespective of the picture it represents. I should add that while the concussion is acute the clinical picture often is subacute and chronic.

I wonder whether classification of coma is wise. It is a symptom, not a syndrome. Coma occurs frequently in all injuries to the head. If deep enough, it bespeaks severe damage of the brain, that is, contusion, laceration and cerebral, subdural, subarachnoid or epidural hemorrhage.

"Punch drunk" is a definite organic syndrome, and the picture is more neurologic than psychiatric. From Martland's work it is known how extensive is the damage to the brain. Patients suffering from it show not only mental symptoms ranging in severity to complete deterioration but tremors and the parkinsonian syndrome.

Some time ago I made the following simple neurologic classification of post-traumatic conditions: 1. So-called concussion, or encephalopathy, which is an organic syndrome characterized by some physical but mostly mental disturbances. 2. Traumatic neurosis. This is rare, and one may quarrel with the concept. In psychoanalytic terminology, one could speak of it as an ego neurosis—what Drs. Bowman and Blau have described as a fright or terror neurosis. This condition does not occur among psychoneurotic persons. Prolonged examination fails to show a neurotic personality. The condition occurs in otherwise intrepid and well adjusted persons. It does not yield easily to treatment. 3. Traumatic psychoneurosis or hysteria, the largest group. In cases of this type it is a question whether trauma to the head is fundamentally concerned with the syndrome. Persons with this disorder use a trauma to any part of the body as a way out of difficulties. Whatever conflict they may previously have had they try to solve by means of the trauma. This explains why a working man who can make $50 a week by working will be content with a compensation of $15 dollars a week, and go on that way for months or years. The trauma is an escape, a way out, an answer to the conflicts. 4. Finally, malingering. This, I agree, is fairly rare, perhaps not more than 1 : 100. Exaggeration of signs and symptoms is very common—in fact, almost universal. True malingering is rarer in the psychoneuroses than in the psychoses.

For the rest, I should like to repeat that the classification, excellent as it is descriptively, seems to me too complex. The value of the paper lies in this, that it presents a common ground for criticism and discussion. It emphasizes the need of speaking a common language. At present, different writers use not only various terms but different concepts. There are concussion neurosis, fright neurosis, neurocirculatory asthenia, post-traumatic state, traumatic neurosis, shell shock and

a host of other verbal labels. One uses the same language for different concepts and expresses the same concepts in different language. While there may not be complete agreement, one should clarify the subject by speaking the same language. From this point of view, the paper presented tonight is important and worthy of a great deal of discussion.

DR. HENRY ALSOP RILEY: I am interested in this presentation because Dr. Brock and I were active in developing the neurologic classification which is included in the "Standard Classified Nomenclature of Disease." I am interested in this particularly from the mechanical side, and shall leave to my confrère, Dr. Wechsler, the more philosophic approach. I do not altogether agree with Dr. Wechsler in objecting to the complexity of this classification. I think classifications are supposed to meet situations, not necessarily preconceived ideas or systems, and any classification must be as complex as the subject matter demands. It facilitates classification and clarifies thinking to have as broad as possible a group of categories and pigeonholes in which one may place conditions; therefore I have no quarrel with the degree to which Drs. Bowman and Blau have expanded this relatively brief classification. There are two or three items I should criticize perhaps. First, I think that as far as is possible all proper names should be eliminated. I suggest for "Korsakoff" some other term, such as "confabulatory"; perhaps some other term would be better. I think the term "epilepsy" should be excluded from this classification. It has been a hobby of mine to war against the term "epilepsy"; when it comes to the convulsive states following injury the term "epilepsy" is used in its least defensible form. The term "convulsion" should be used, as it is with any neurologic disease in which there is a convulsive state.

I have a definite feeling against use of the term "punch drunk." I think it is too colloquial and slangy; the condition in its acute form could be called "diffuse cerebral ecchymoses," or a term which carries the same connotation; for the chronic state some other term could be elaborated. As for the chronic forms of mental disorders, it would be wise to separate the functional and the organic types and place them in separate groups. As I remember it, in the last group the authors included both organic and functional reaction types, which I think is confusing.

With regard to the term "anxiety neurosis," we tried to get away from the term "neurosis" in the neurologic classification. We used "anxiety state" or "anxiety hysteria," either of which is better, I think, than "anxiety neurosis."

These are the only suggestions I have to make. As I said before, I think this is a great step forward as compared with the meager possibilities of the former classification, and I do not object in any way to its expansiveness.

DR. KARL M. BOWMAN: I agree that whenever possible one should avoid proper names and use some other term. Epilepsy is a discredited term, and I agree that it is preferable to use one of the other terms which is being substituted for "epilepsy."

One of the difficulties in making a classification is that one may use essentially a psychiatric or a neurologic approach; this classification is made from the former. Either approach does violence to the other. We said in the beginning that an etiologic classification was most desirable, and then, after the first two main headings, we deviated more or less from the etiologic to a descriptive classification, with the definite statement that we were using the concept of certain syndromes or reaction types, rather than actual etiologic concepts. I should like again to emphasize that fact, because I think the discussers spoke as though we had tried to make some of the terms etiologic, when we had specifically said we were making them represent reaction types.

DR. ABRAHAM BLAU: I want to thank Dr. Wechsler and Dr. Riley for their comments. I agree with Dr. Riley about the need for some complexity in the classification. A simpler type of classification, as proposed by Dr. Wechsler, is inadequate because, for example, the term "concussion," or "traumatic encephal-

opathy" thus includes a heterogeneous group of conditions which should be designated by several terms. With regard to whether traumatic coma should be separated as a syndrome, we see many cases that have to be classified in this way from a psychiatric point of view. Traumatic coma is as much a syndrome as is, for instance, traumatic delirium.

I agree with Dr. Riley that epilepsy is a poor term, and we should substitute "convulsive disorder." In relation to the Korsakoff syndrome, which uses a person's name, one must admit that the syndrome is so well known in this way that it would be difficult to substitute another designation. The term "amnesic syndrome" has been suggested in the German literature. The question whether the term "punch drunk" should be retained or whether the condition should rather be called "traumatic encephalopathy of pugilists" is debatable. The condition is well known in the literature under the name "punch drunk," even though the term is colloquial. Furthermore, the basic principle in classification is to use the shortest term which gives some idea of the nature of the syndrome.

Book Reviews

Grundformen der Affektivität (Die Zustandsgefühle beim gesunden und kranken Menschen). By Walter H. von Wyss. Price, 13.60 Swiss francs. Basel: S. Karger, 1938.

The impression that one gains in reading this unusual and stimulating treatise on the basic forms of affective response is that of a wealth of ideas constructed on the basis of a somewhat superficial skimming of the varied methods of approach to this field. The fundamental features of the monograph could be expressed as consisting of three motives, which run through the whole exposition. First, there is the attitude that is best expressed in the quotations from Pascal, which are found in the opening and concluding paragraphs of the book and which stress the fact that feeling or sentiment or instinct (the three being used more or less interchangeably) is more fundamental in human contact and the appreciation of one's status in the environment than is the faculty of logical reasoning, which is a somewhat superficial and flimsy instrument as compared with feeling. Second, the function of feeling is an expression of the whole organism, and not of any particular part of it, so that various states, such as hunger, thirst, pain and exhaustion, are expressive of a reaction of the whole organism to a given stimulus or setting rather than that of any particular organ. Third, although the author is trying to escape the teleologic evaluation of feelings, he consistently points out, nevertheless, that feeling of any type is expressive of either a state of well-being in the organism or an absence of it.

In a fundamental classification of feelings, the author alines himself with Scheler and others of the phenomenologic school, grouping them, first, as the sensory and the vital and, second, as the spiritual or social. A broad description is then undertaken of the various forms of outward expression of feelings, including visible reactions, such as facial expressions and gestures, and the less easily observed changes in the vegetative nervous system and bodily fluids. The main feature of this description is the point of view that these expressions are to be regarded not as a cause or effect but as an integral part of the feelings.

Following this is a description of the various feeling states, beginning with pain and continuing to the so-called vital or life feelings, such as hunger, thirst, nausea, fatigue and exhaustion, vertigo and euphoria. Then there are a chapter on states of anxiety and one on joy and sadness. The concluding chapters deal with the relation between feeling and the nervous system, in which most prominent attention is given to the current physiologic approaches and to the theory advanced by von Monakow. Finally, a chapter is devoted to the picture language of the feelings, with particular prominence given to the theories of Klages and Bergson.

One of the most impressive features of the monograph is that it is written from the point of view of the medical man in dealing with disturbances in feeling as they occur in various types of physical illnesses, it being emphasized that in sizing up the occurrence of such disturbances in a sick person one should take into consideration his emotional reactions to the illness as much as one does the various disturbances in the other functions of the organism.

Out of the Running. By G. Gertrude Hoopes. Price, $2. Pp. 158. Baltimore: Charles C. Thomas, Publisher, 1939.

This is an autobiography of a woman with congenital cerebral palsy. Although mentally superior, she was greatly handicapped physically, being practically unable

to walk and incapable of articulate speech. She learned to communicate by sign language and to type with one finger, after which her progress in acquiring information was rapid. Although the development of intelligence is ordinarily considered to be highly dependent on motor capacity and speech functions, the author's achievements illustrate the possibility of a rich mental development in the absence of vocalization and motor skill. Her story is a clear account of her emotional and personality development and of her attitudes and experiences. With rare insight she describes her growing consciousness, at adolescence, of her physical limitations, the period of mild depression she experienced at the age of 15 and of her religious conversion at 20. Her vivid description of energetic repression of sensitiveness to her condition, of resignation to her limitations and of humorous and courageous overcoming of pessimism and doubt is not only a document of interest to psychologists and psychiatrists but a challenge and comfort to all physically handicapped persons.

Outline of Psychiatric Case-Study. By Paul W. Preu, M.D. Price, $1.85. Pp. 140. New York: Paul B. Hoeber, Inc., 1939.

This book presents a detailed outline of instruction intended for the physician beginning training in psychiatry. It includes not only suggestions as to practical technics in making a thorough psychiatric study but also a rather comprehensive survey of material to be obtained from anamnesis, mental examination and clinical observation. Emphasis is placed on careful, orderly recording, not merely of the results of the history taking and of the mental status but of all contacts between the patient, his relatives and the hospital staff, which is so often inadequately done in psychiatric institutions. The implied theoretic orientation is not toward any specific school of thought. Dynamic concepts are evident, but the formal descriptive attitude probably necessary for the beginner's initiation is dominant. The book impresses the reviewer as a valuable addendum to the library of a training institution, which may prove useful as a time-saving device for the senior resident or clinical director responsible for teaching elementary technics to the novice.

CORRECTIONS

In the article by Dr. James L. Poppen entitled "Ligation of the Left Anterior Cerebral Artery: Its Hazards and Means of Avoidance of Its Complications," which appeared in the March issue (ARCH. NEUROL. & PSYCHIAT. **41**:495, 1939), the word "Mayo" in the first line of the third paragraph on page 498 should read "Lahey," and the first word, "left," in the next line should be eliminated.

In the paper by Drs. Frederick P. Moersch and James W. Kernohan entitled "Hemiballismus: A Clinicopathologic Study," in the February issue (ARCH. NEUROL. & PSYCHIAT. **41**:365, 1939), the infarct in the authors' case should have been described as appearing in the right, rather than in the left, corpus Luysi.

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